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CERVICAL ARTHROPATHY IN SYRINGOMYELIA, TABES DORSALIS AND DIABETES

BY

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VERY few references to arthropathy of the cervical spine are to be found in the literature: indeed arthropathic lesions of the spine in general have not been very fully studied, and such references as exist are concerned almost solely with tabetic arthropathy. Tabetic spinal arthropathy began to attract attention at the beginning of this century, partly, probably, as a result of the introduction of X-rays. The first systematic study was made by Abadie (1900) who collected 9 cases from the literature and the museum of the Salpêtrière and added 5 personal cases. There were three autopsies. He alludes only briefly to the cervical vertebræ, which, he says, show only slight changes. Arthropathic degeneration increases as one descends the spine, assuming its characteristic form in the lower dorsal and lumbar vertebræ.

Garvey and Glass (1927) report 4 cases of tabetic arthropathy of the lumbar spine, and the same authors (Garvey and Glass, 1928), adding 4 more cases, state that the highest vertebra to be affected in their series was the eleventh dorsal. Stekolnikow and Freidowitsch (1929) say that in their series of tabetics arthropathic changes in the spine were limited to the lumbar region, except in one case in which the lower dorsal region was involved. Mann (1935) says that arthropathy of the spine is rare in tabes, occurring usually in the lumbar spine: in the cervical region it is very rare. Steindler, Williams and Puig-Guri (1942) found 214 arthropathic joints in 134 tabetics. In only 14 (10·4 per cent) was the spine involved, in the thoracic or lumbar regions. No case of cervical arthropathy was observed. Møller (1945) relates spinal arthropathy in tabes to the tendency to spontaneous fractures. Holland (1952) reports 1 case and (1953) 5 cases, and Campbell and Doyle (1954) report 8 cases, all of lumbar arthropathy.

References to syringomyelic spinal arthropathy are even scantier.

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Garvey and Glass (1928) in their paper on tabetic spinal arthropathy comment that in syringomyelia, in which the lesion involves predominantly the cervical cord, the accompanying arthropathies are found in the higher divisions of the spine and the upper limbs. Gagel (1936) mentions one instance of degeneration and narrowing of intervertebral discs in the lumbar spine in syringomyelia. Zucker and Marder (1952) report one case of arthropathy of the lumbar spine in diabetes.

Our own material consists chiefly of 52 cases of syringomyelia, but we have also studied a few cases of cervical arthropathy in tabetics and diabetics. Only in syringomyelia does arthropathy of the cervical spine occur with sufficient frequency to make it possible to study its causes. For the last ten years we have X-rayed the cervical spines of all our patients with syringomyelia. Thus the selection of cases was based upon an initial clinical diagnosis of syringomyelia. This point is stressed because, as will be seen, the X-ray changes in the cervical spine were often indistinguishable from those found in cervical spondylosis. Clinically, however, syringomyelia and cervical myelopathy due to spondylosis are unlikely to be confused with one another today.

For the purposes of the investigation we found it necessary to classify the X-ray changes found in the cervical spine, especially with reference to their grades of severity. In group 1 we placed those patients with changes so slight that it seemed unlikely that they were of any clinical significance. In group 2 we placed those with a moderate degree of articular change, such as narrowing of intervertebral disc spaces with moderate posterior osteophytes and degenerative changes in the uncovertebral joints. In group 3 we included those patients with more severe changes, the intervertebral discs being grossly degenerated or having almost disappeared, and the osteophytes being unusually large, especially at the lateral margins of the vertebræ. We have disregarded for the purposes of this investigation those patients in group 1: when, therefore, we speak in this paper of patients with X-ray changes we are referring only to those whose cervical spines were sufficiently abnormal to bring them into groups 2 or 3.

Age and Sex Distribution

Fig. 1 shows the age and sex distribution of the 52 cases of syringomyelia. There were 19 males and 33 females.[1] 11 of the 19 males showed X-ray

[1]The predominance of females in our series is contrary to past experience in syringomyelia. Gagel (1936) quotes three earlier series in which males exceeded females in the proportion of 5 to 3. We have therefore investigated the sex ratio of patients with syringomyelia admitted to the London Hospital during the last thirty years. It is as follows: 1925–1934, males 49 per cent, females 51 per cent. 1935–1944, males 45·3 per cent, females 54·7 per cent. 1945–1954, males 38·2 per cent, females 61·8 per cent.

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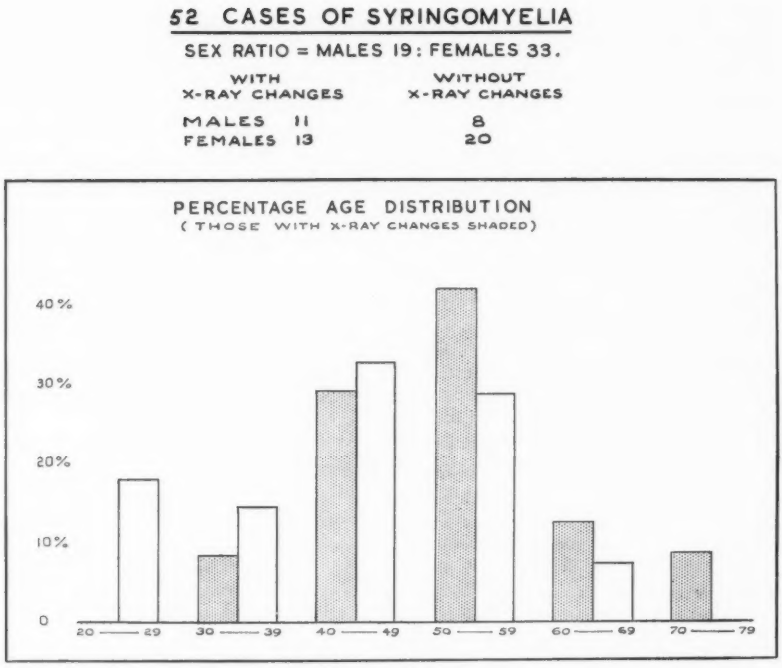

FIG. 1.—Sex incidence and percentage age distribution of X-ray changes in the cervical spine.

changes and 8 did not, while of the 33 females only 13 showed X-ray changes. Thus X-ray changes were considerably more likely to occur in males than in females. But it is noteworthy that more than half the patients with syringomyelia showed no significant X-ray abnormality in the cervical spine.

Fig. 1 also shows the percentage age distribution. Patients with X-ray changes show a significant peak in the fourth and fifth decades, whereas the age distribution of those without X-ray changes is more widely scattered. Since the correlation between the incidence of X-ray changes and the age of the patient might be due merely to the fact that the older patients had had the disease longer than the younger ones, the average duration of symptoms of patients with and without X-ray changes was estimated, and it was found, as is shown at the bottom of the table, that patients

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with X-ray changes had had symptoms of an average duration of 8·7 years, while those without X-ray changes had had symptoms for an average of 10·2 years. The length of the history, therefore, is not a significant factor in relation to the occurrence of X-ray changes.

Relationship Between X-ray Changes and Neurological Symptoms

The next step was to investigate whether there was any relationship between the occurrence of X-ray changes in the cervical spine and the patient's neurological condition. It has long been thought that there is a relationship between the occurrence of neuropathic joints and loss of sensation. To investigate this in relation to cervical arthropathy we classified our 52 patients according to the extent of their cutaneous analgesia, as loss of pain sensibility has generally been held to be the important factor. The results are shown in Table I. In this table the maximum

Table I.—Relation Between X-ray Changes and Analgesia

	Percentage Distribution				
	Analgesia of all cervical segments on both sides	*All on one side: some on the other*	*Some on both sides*	*All on one side: none on the other*	*Some on one side: none on the other*
With X-ray changes	29	8	42	4	17
Without X-ray changes	39	14	14	29	4

Table II.—Relation Between X-ray Changes and Lower Motor Neurone Lesions

	Percentage Distribution					
	Wasting and weakness of—all cervical segments on both sides	*All on one side: some on the other*	*Some on both sides*	*All on one side: none on the other*	*Some on one side: none on the other*	*None*
With X-ray changes	33	4	21		29	12
Without X-ray changes	4	7	29	4	48	7

area of analgesia is shown in the left-hand column and the minimum in the right-hand column. The severity thus diminishes from left to right. This table shows that the patients with the most extensive cutaneous analgesia are not more likely to show X-ray changes in the neck than those with less, but there may be a slightly greater tendency to those with

cutaneous analgesia on both sides to do so, since both sides were affected in 79 per cent of those with X-ray changes and in only 67 per cent of those without.

Table II shows the relationship between the X-ray changes and the extent of the lower motor neurone lesions. Here, again, the cases have been arranged in relation to the extent of the lower motor neurone lesions in terms of the number of cervical segments involved. This table shows a correlation between the extent of the lower motor neurone lesions and the presence of X-ray changes, but it provides no evidence as to whether one is the cause of the other, a point which we shall discuss later.

Age Distribution of X-ray Changes in Syringomyelia Compared With That of Cervical Spondylosis

Fig. 2 shows the age distribution of patients suffering from syringomyelia

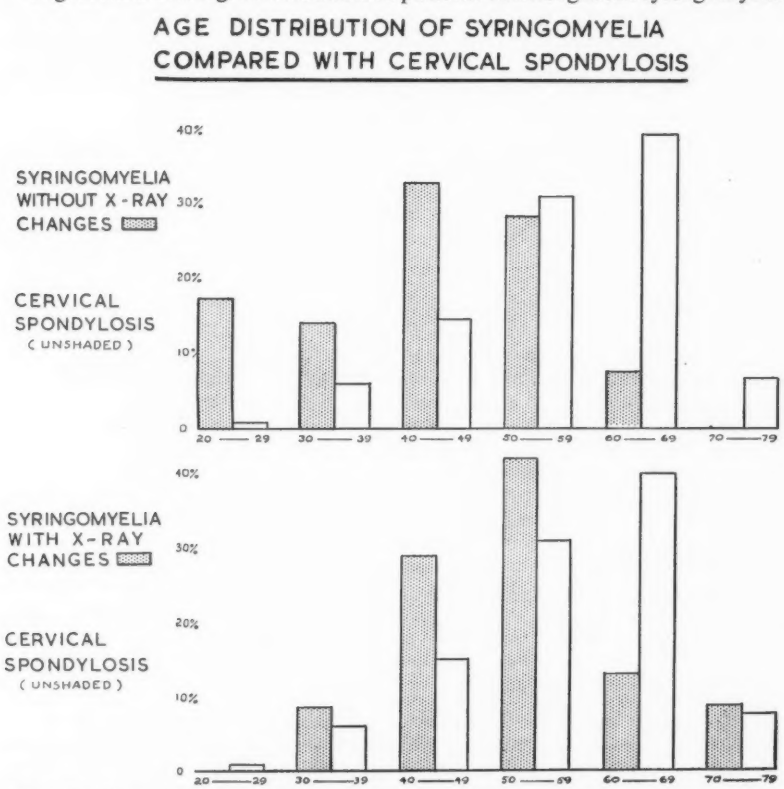

FIG. 2.--Percentage age distribution of patients with syringomyelia with and without X-ray changes in the cervical spine compared with that of patients with cervical spondylosis.

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with and without X-ray changes in the cervical spine, and that of cervical spondylosis obtained from a series of 100 consecutive cases. In the upper half of the figure a comparison between cases of syringomyelia without X-ray changes and cases of cervical spondylosis shows no correlation. In the lower half of the figure cases of syringomyelia with X-ray changes are compared with cases of cervical spondylosis and this figure shows that the curve of age distribution of the cases of syringomyelia is similar to that of the cases of cervical spondylosis except that it is shifted one decade to the left. This, however, is due to the fact that the age distribution of the patients with syringomyelia was lower than that of those with cervical spondylosis. When correction is made for this, the age incidence of X-ray changes in the two groups is identical.

Illustrative Cases

Case 1 is a patient who had had syringomyelia for twenty-three years. X-rays of her neck taken twelve years and twenty-two years after the onset show how slight and how slow the degenerative changes can be.

Case 1.—Female, aged 49, L.H. No. 24540/49.

History.—Twenty-three years ago she was first an in-patient at the London Hospital where she was treated for brachial neuritis. In 1937 she developed sensory loss over the ulnar side of the right arm and at that time her arm-jerks were found to be absent. In 1949 she noticed that the fingers of her left hand had become weaker and that she was developing a claw hand. At that time she had analgesia and impaired appreciation of heat and cold over the ulnar border of her left hand, and to a less extent of the right, with absent arm-jerks and a mild spastic paraplegia. She was given a course of deep X-ray therapy with some improvement. In 1951 she had a fall and injured her face, following which she had some pain in her shoulders and her left hand became weaker and she was given a second course of deep X-ray treatment. After this, however, she gradually deteriorated until July 1954, when she said that her right hand was becoming weaker and she complained of a pain in the right side of her face.

Examination.—In January 1958 her cranial nerves were normal except for nystagmus. She had marked wasting and weakness of the left hand with a flexor contracture and slight wasting and weakness of the right hand, together with slight spastic weakness of both lower limbs. There was impairment of appreciation of pin-prick, heat and cold extending over the fourth to eighth cervical segmental areas, more marked on the left side than on the right. The tendon reflexes in the upper limbs were absent, the knee and ankle jerks were exaggerated and both plantar reflexes were extensor.

X-rays of cervical spine.—X-rays taken in 1947 (fig. 3, Plate XXXI) show only slight narrowing of C6–7 intervertebral disc space together with slight lower cervical kyphosis. X-rays taken ten years later in 1957 (fig. 4) show that the C6–7 space has become much narrower, while the body of C6 has become narrower from above downwards and elongated antero-posteriorly. The kyphosis is more marked and the whole cervical spine shows some degree of osteoporosis.

Case 2 is a patient with twenty-eight years' history of syringomyelia leading to spontaneous dislocations of both shoulders which are arthropathic. X-rays of her cervical spine, taken twenty-five years after the onset, show changes of moderate severity.

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Case 2.—Female, aged 70, L.H. No. 7012/55.

History.—Twenty-eight years ago she developed occasional numbness in the left hand. Twenty-one years ago she began to notice weakness of both legs and complained of low backache. She also began to burn herself without noticing it. Syringomyelia was diagnosed and she was given a course of deep X-ray treatment to the cervical spine. Following this her condition improved. Nineteen years ago she dislocated her right shoulder by lifting a saucepan: this dislocation was painless. Sixteen years ago her legs again became weak and she had a further course of deep X-ray treatment, and again her condition improved. Over the next few years her condition once more deteriorated and she was then given a third course of deep X-ray treatment. Four years ago she dislocated her left shoulder while raising her arm. This required surgical reduction. After this she remained fairly well until three years ago when she tripped and fell forwards, striking her head. The following day both hands felt strange and stiff and she found that she had completely lost the feeling in them.

Scars of burns, both old and recent, on her chest, back and hands. Slight limitation of neck movements. Dorsal kyphoscoliosis with lumbar lordosis. Right shoulder completely disorganized with grossly increased mobility. The head of the right humerus could not be palpated. Left shoulder dislocated; head of humerus palpable. Bilateral osteoarthritis of knees.

Cranial nerves normal. Gross wasting and weakness of muscles of both shoulders. Moderate weakness of movements of the elbows and wrists. Severe weakness and wasting of small muscles of both hands. Unable to abduct her shoulders, partly because of weakness and partly because of arthropathy. Upper limbs hypotonic. Lower limbs, bilateral spastic weakness, more marked on left side than right. Sensation: complete loss to light touch over the palm and dorsum of both hands up to the wrist and impairment over the distal third of both fore-arms. Extensive loss of appreciation of pain, heat and cold. On the right side the loss is most severe from C2 to D10 with less severe impairment from D10 to L3. On the left side the loss is most severe from C5 to D10 with less severe loss from D12 to L5. Vibration sense: normal in clavicles, absent in the upper limbs and left leg and ? just perceived at the right knee. Postural sense: impaired in both upper limbs, normal in both lower limbs. Reflexes: arm-jerks and abdominal reflexes absent, knee and ankle jerks exaggerated, plantars extensor.

X-rays.—Cervical spine (figs. 5 and 6): narrowing of intervertebral disc spaces with anterior and posterior osteophytes between C4 and C5 and C5 and C6. Some sclerosis of vertebral bodies, especially C5. Right shoulder: the head of the right humerus is missing and there is calcifying debris in the surrounding region. Left shoulder: there is flattening of the head of the left humerus. Both shoulder-joints are arthropathic.

Case 3. This patient had had syringomyelia for over twenty years. Twenty years previously she had had a cervical laminectomy. X-rays of her cervical spine, taken fourteen years and twenty years after her operation, showed severe and increasing arthropathic changes.

Case 3.—Female, aged 53.

History.—Twenty years ago she had a cervical laminectomy for symptoms of lesion involving her cervical spinal cord. Sixteen years ago she noticed that her left foot began to turn in. Over the next few years weakness in her left upper and lower limbs became progressively worse and she developed pains in her head and neck. Her hands became numb and painful and she occasionally burned the right hand without noticing it. The right leg also became numb. She has had some precipitancy of micturition.

Examination.—Cranial nerves normal. No wasting or weakness of right upper limb.

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In the left upper limb there was wasting and weakness, mainly of the muscle groups supplied by the eighth cervical and first dorsal segments. There was slight weakness of movements of the left elbow and shoulder. There was spastic weakness of both lower limbs, more marked on the left side than on the right. The biceps, supinator and triceps jerks were brisker on the right side than on the left, the knee and ankle jerks were brisker on the left side than on the right and both plantar reflexes were extensor. Relative analgesia and thermo-anæsthesia were present over the right side of the body below C6 and from C6–D2 on the left side. There was loss of postural sensibility in the digits of the right hand and toes of the right foot. Arthropathic changes were present in the finger-joints of the right hand.

X-rays.—X-rays of the cervical spine were taken in 1947 (fig. 7) and 1953 (fig. 8). Gross changes are present at all joints of the cervical spine which had progressed even farther in the later view. Between C5 and C6 the intervertebral disc space has disappeared and that between C4 and C5 has almost disappeared. The other intervertebral disc spaces are narrowed. Anterior and posterior osteophytes are present and the alignment of the vertebræ disorganized. It is probable that the laminectomy contributed to the exceptionally severe degeneration.

Case 4. A man aged 48 had had syringomyelia for sixteen years. Eleven years after the onset his neck was X-rayed and showed only some limitation of flexion and extension associated with some narrowing of C5–6 disc space. Five years later there were severe degenerative changes and a myelogram showed multiple filling defects due to disc protrusions.

Case 4.—Male, aged 48, L.H. No. 1220/56.

History.—Sixteen years ago he was involved in a car accident in which he cut his head and was slightly concussed. About that time he noticed loss of sensation of heat and cold in the left hand, and that he burnt it without feeling pain. Six years ago he noticed weakness of the left hand and twitching of the muscles of the left arm. He was admitted to hospital and found to have weakness of all movements of the left upper limb, the extensor groups being more affected than the flexor. The small muscles of the hand were particularly weak. There was marked wasting of the small muscles of the left hand and the left triceps, and moderate wasting of the forearm and arm on that side. Fasciculation was seen in the muscles of the left upper limb. The right upper and both lower limbs were normal. Both biceps-jerks and the left triceps-jerks were absent and the left supinator jerk diminished. The knee-jerks were present and equal and the ankle-jerks diminished. The left abdominals were absent. The right plantar was flexor and the left a doubtful extensor.

There was impairment to pin-prick over C3–D12 dermatomes on the left and absence of temperature appreciation over C4–C8 on the left with impaired temperature sense over C2 and 3. Light touch was normal. Vibration sense was absent below the left clavicle and at the right wrist.

Investigations.—C.S.F.—pressure 160 mm. Free rise and fall on jugular compression. Cells 1 per c.mm., protein 25 mg. per cent, W.R. negative, Lange normal.

X-ray.—Cervical spine. Movement of flexion and extension is somewhat limited. No bony abnormality detected but there is some diminution of the C5–6 disc space. He was given a course of deep X-ray therapy (estimated cord dose of 1,500 r). His condition continued to deteriorate in spite of this treatment and when he was seen three years ago he had weakness and wasting affecting chiefly the flexors of the wrist and fingers and the small muscles of the hand on the left side and could not close his

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left hand. The characteristic sensory loss extended from the face to just below the groin on the left. He had an ulcer on the left forearm. The supinator and biceps-jerks on both sides were absent and the left triceps-jerk was diminished. The left knee-jerk was brisker than the right, the right ankle-jerk was just present and both plantars were flexor. He was given a second course of deep X-ray therapy to the cervical and dorsal cord to a tumour dose of 1,000 r in ten treatments. Following this treatment his condition improved and he remained fairly well until just before admission when after an afternoon nap he found on awakening he could not lift his left arm. This arm felt dead for about two hours and for the next few days his left shoulder felt numb and he did not know where his shoulder and hand were. After a few days his condition gradually improved until he was able to lift his arm again.

Examination.—The fundi and other cranial nerves were normal. Cervical movements slightly limited, full flexion causing aching pain in the neck. There was marked wasting and weakness with fasciculation of the muscles in the left upper limb with winging of left scapula. There was some wasting of spinati on right. There were analgesia and thermo-anæsthesia from C2–D12 on left and from C3–D8 on right. Vibration sense was absent at left wrist and impaired at left elbow and clavicle. Postural sense was absent in fingers of left hand, present at wrist. The biceps-jerk, triceps-jerk and supinator-jerk were absent on left. Right biceps-jerk absent. Right triceps-jerk present. Right supinator-jerk inverted. Knee and ankle jerks sluggish and equal. Plantars—right flexor, left extensor.

Investigations.—C.S.F.—pressure normal. Protein 20 mg. per cent, W.R. and Lange negative.

X-ray cervical spine.—Degeneration of the discs between C3–4, C4–5, C5–6 and C6–7. Hypermobility of C2 on C3 on flexion of the cervical spine.

Myelogram (figs. 9 and 10).—Transverse bars protruding from C3–4, C4–5 and C5–6 discs. The antero-posterior view shows filling defects at C3–4, C4–5 on the left and on the right C4–5 and C5–6.

Case 5 is a tabetic in whom sensory and motor radicular symptoms were caused by arthropathy of the cervical spine.

Case 5.—Male, aged 58, L.H. No. 19773/50.

History.—In 1918 he developed a primary chancre for which he was treated and his Wassermann reaction was said to be negative two years later. He remained well until 1937 when he developed lightning pains and two years later his gait became unsteady. Four months before his first admission to hospital in 1945 he developed pains in the lower part of his back. At that time his blood W.R. was positive and the c.s.f. showed 3 cells per c.mm., protein 30 mg. per cent, Lange 1122210000, W.R. negative. He was treated with bismuth intramuscularly. After this he remained fairly well for four years, but then noticed a gradual onset of tingling and numbness in the fingers, that his hands were becoming clumsy and his grip weak. His walking, also, became more unsteady and at the time of his second admission in 1950 he could walk only a short distance with the aid of a stick.

Examination.—His pupils were irregular and the left was larger than the right. Neither reacted to light, but both on accommodation. There was slight right ptosis. The other cranial nerves were normal. In the upper limbs there was marked wasting and weakness of the shoulder girdle muscles, more severe on the left side than on the right, and there was generalized weakness of both lower limbs. All four limbs were hypotonic. Sensation: in the upper limbs there was impairment of appreciation of pin-prick at the tips of the fingers, together with loss of appreciation of passive movement in the fingers. Vibration sense was impaired below the costal margins and in the lower limbs there

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was relative analgesia with delayed appreciation of pin-prick and a delayed withdrawal reflex. The tendon reflexes in the upper limbs were sluggish, the knee and ankle jerks were absent and the plantar reflexes were extensor. This time the W.R. was negative in the blood and C.S.F. and the C.S.F. was otherwise normal.

X-rays of cervical spine.—Figs. 11 and 12 show the severe degenerative changes in the cervical spine in 1950 and figs. 13 and 14 a considerable increase in the extent and severity of the changes by 1954. This patient also had arthropathy of the lumbar spine.

Subsequent history.—After discharge from hospital his walking continued to be unsteady and he complained of shooting pains all over the body. In June 1951 he developed what he called "rheumatic" pains in the left upper limb extending from the shoulder to the elbow coming on in spasms and lasting from 5 to 10 minutes at a time and occurring several times a day. When the pain was severe his arm became useless. He was again admitted to hospital in October 1952, and it was found that his upper limbs were weaker and more wasted than on the previous admission. He was fitted with a collar and was kept under observation for the next three years, during which the pains persisted.

Case 6 is a tabetic in whom an almost complete flaccid paralysis of the upper limbs was due in part to arthropathy of the cervical spine and in part to arthropathy of both shoulders.

Case 6.—Male, aged 69, L.H. No. 17358/57.

History.—In 1924 he developed severe pains in his back and both lower limbs. The latter became weak and occasionally gave way. He was diagnosed as suffering from neurosyphilis and was treated with injections. After this the pain and weakness improved for a time, and he remained at work until 1940 when he fell down some steps and fractured his right hip. This necessitated his staying in bed for a few weeks, and when he got up he found walking very difficult and started to use a wheeled chair. In 1941 he fell out of his chair and fractured his right shoulder and a few months later he again fell out of his chair and fractured his left shoulder. Since then he has noticed wasting of the muscles surrounding the joints and found that he could not control movements at the joints. He continued to have backache and shooting pains in the legs until three years ago when his doctor treated him with penicillin. More recently he has had pain in his neck, both shoulders and down both arms. In September 1956 he was found to have an enlarged prostate and a transurethral section was done. Before that he had been incontinent of urine, but at the time of admission was continent. For four or five years he had had severe cramp-like pain in the right big toe which had been gradually getting worse and when the pain was severe his toe became dorsiflexed. At the time of admission he was unable to walk and his arms were so weak that he could not manage his wheeled chair or feed himself.

Examination.—Bilateral ptosis and Argyll-Robertson pupils. Otherwise his cranial nerves were normal. There was extreme wasting and weakness of the upper limbs, most marked in the muscles enervated by the fifth cervical segment. There was abnormal mobility of both shoulder-joints. There was moderate weakness of both lower limbs. Vibration sense and position sense were absent in both upper and lower limbs. There was relative analgesia over both lower limbs. Over the right great toe and outer border of the right foot and adjacent toes the threshold to pin-prick was raised and there was a delay of two or three seconds between a pin-prick and awareness of the sensation. The triceps-jerks were just present, all other tendon reflexes were absent and the plantar reflexes were not obtained.

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Investigations.—His blood W.R. was negative. His C.S.F. was normal in all respects with a negative W.R.

X-rays of cervical spine.—The cervical spine showed severe and extensive degenerative changes, and both shoulders and the right hip were also arthropathic.

The Nature of Cervical Arthropathy

What are the X-ray appearances characteristic of arthropathy of the cervical spine? If we interpret this to mean, what are the X-ray changes in the cervical spine sometimes found in syringomyelia or tabes, and such that the radiologist would unhesitatingly describe them as arthropathic, the answer must be that in such cases the bodies of the vertebræ may be expected to show a considerable degree of osteoporosis, and they will tend to be flattened from above downwards, and somewhat lengthened anteroposteriorly. The intervertebral discs will tend to be narrowed almost to the point of disappearance. Osteophyte formation will be present, and lateral osteophytes, in particular, are likely to be florid. Finally, these changes are often present at all articulations from the second cervical to the first dorsal vertebra. Examination of a number of patients with syringomyelia, however, and of the same patient over a number of years, shows that the changes just mentioned, which would unhesitatingly be described as arthropathic, are the final stages of a process which earlier in its course is indistinguishable from cervical spondylosis occurring in patients who do not suffer from syringomyelia (*see* figs. 3 to 6). Moreover, none of the severe "arthropathic" changes just described is pathognomonic of either syringomyelia or tabes, since identical changes are to be found in advanced cases of cervical spondylosis. From this we conclude that the X-ray changes in the cervical spine described as "arthropathic" are radiologically only an exceptionally severe and extensive degree of the changes with which we are familiar in cervical spondylosis. Nor is there any pathological evidence which enables us to differentiate them.

The X-ray changes in the cervical spine in syringomyelia have an age distribution which resembles that of cervical spondylosis. The ratio of males to females with cervical spondylosis is 2·2:1 (Brain, Northfield and Wilkinson, 1952): the probability that a male with syringomyelia will develop cervical arthropathy compared with a female is 2·1:1. Taking into account the fact that over 50 per cent of patients with syringomyelia show no abnormality in the X-rays of the cervical spine, although they have suffered from the disease as long as those who do, it seems reasonable to infer that it is not the syringomyelia which determines whether or not the X-ray changes occur, but that the same causes which lead to cervical spondylosis in normal individuals also operate to produce the X-ray changes which are found in syringomyelia and we have no evidence that they occur with greater frequency in patients with syringomyelia than in the rest of the population. But it would appear that if they occur

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in syringomyelia or tabes they are likely ultimately to reach a more severe degree of degeneration. In the earlier stages the X-ray changes are identical with those of cervical spondylosis, and it is only in advanced cases that a degree of degeneration occurs which is both more severe and more extensive than is commonly observed in uncomplicated cervical spondylosis, though exceptionally it may also be found in this condition (figs. 15 and 16).

What, then, is the factor in syringomyelia and tabes which accelerates the changes of cervical spondylosis in such patients and produces such a severe end-result? Table I shows that there is no correlation between the severity of the analgesia measured by its extent and the occurrence of the X-ray changes, except that the X-ray changes seem somewhat more likely to occur in patients with bilateral sensory loss. The negative correlation with the severity of the analgesia, however, should not be taken to imply that the analgesia plays no part in the pathogenesis of the degeneration of the spine, since some analgesia was present in all cases. We see no reason to reject the traditional view that the analgesia is a factor, and it is probably responsible for the severity of the degeneration in these cases, because the patient, having lost the protective effect of pain, subjects the already damaged joints to further trauma as a result of movements which would not readily occur if they were painful. In the present state of our knowledge, however, it is impossible to exclude a local "trophic" factor, which might be related to loss of axon reflexes.

It has been suggested that the liability to spinal arthropathy may be related to occupation, heavy labour being a contributory factor. In our series of syringomyelics, however, there was no difference in this respect between the patients with arthropathy and those without; and a history of trauma was not obtained significantly more often in the arthropathic group.

The correlation between the occurrence of X-ray changes in the cervical spine and the severity of the lower motor neurone lesions, shown in Table II, was an unexpected finding. It is possible that weakness of the cervical muscles indirectly increases the stress upon the intervertebral joints. Even if this is so, however, it is also possible that the lower motor neurone lesions are themselves in part the result of the changes in the spine, which cause compression either of the syringomyelic spinal cord or the anterior roots in the intervertebral foramina.

Cervical Arthropathy in Tabes Dorsalis

We have seen cervical arthropathy in 11 cases of tabes dorsalis. We believe its pathogenesis to be the same as that of cervical arthropathy in syringomyelia. Since in tabes the analgesia tends to occur earlier and more extensively over the trunk and lower limbs than over the upper limbs

spinal arthropathy in tabes tends in contrast with syringomyelia to be encountered more often in the dorsal and lumbar spine than in the cervical. In the dorsal spine it may lead to compression of the spinal cord and in the lumbar spine to compression of the lumbosacral nerve roots.

The older writers on syphilis laid stress upon a lesion described as syphilitic spondylitis (Neumann, 1904; Ziesche, 1911; Sgalitzer, 1941; Freedman and Meschan, 1943; and Epstein, 1955). Syphilitic spondylitis, thought to be due to direct invasion of the spine by the causal organism, was said to be particularly common in the cervical region. In Neumann's series of 55 cases the cervical spine was involved in 36 and 70 per cent of Ziesche's cases were in this region. From the accounts given it is often difficult to distinguish this "syphilitic spondylitis" from cervical spondylosis or arthropathy occurring in patients suffering from syphilis.

Some of the X-rays illustrating Freedman and Meschan's article appear indistinguishable from cervical spondylosis and these authors stress the difficulty of diagnosing syphilitic spondylitis. However, the calcification of the anterior and lateral ligaments, which they describe and illustrate, associated with complete ankylosis of the spine, recalls ankylosing spondylitis and is unlike anything seen in spondylosis or spinal arthropathy. We have never encountered syphilitic spondylitis, and it is not recognized today by those radiologists and venereologists of whom we have made enquiry.

Cervical Arthropathy in Diabetes

One of us has long held the opinion that diabetics are prone to particularly severe and extensive degenerative changes in the spine, and has drawn attention to the occurrence of lesions of spinal roots as a result (Brain, 1951). Foster and Bassett (1947) have reported instances of arthropathy associated with diabetic neuropathy, and Zucker and Marder (1952) have described a case of Charcot's spine in diabetes. We have seen a number of instances of spinal arthropathy in diabetes, the cervical and lumbar regions being most frequently involved. When the joints of the limbs become arthropathic in association with lesions of the peripheral nerves in diabetes it is probable that analgesia plays an important part in the causation, as in syringomyelia and tabes dorsalis. There is less evidence for this in the case of the spine, especially the cervical spine, since cervical arthropathy may occur in diabetes with little or no evidence of sensory loss in the upper limbs. It is probable, therefore, that some metabolic factor associated with the diabetes renders the intervertebral discs particularly prone to degeneration.

The Clinical Significance of Cervical Arthropathy

Since cervical arthropathy occurs in three diseases, syringomyelia, tabes dorsalis and diabetes, all of which are characterized by lesions of the

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nervous system, it is easy to overlook the fact that some of the symptoms of which the patient complains may be due to the cervical arthropathy or that the cervical arthropathy is responsible for exacerbating the disorder which is its cause. These points were illustrated by patients in our series. In Case 4, a patient with syringomyelia, in whom a myelogram showed compression of the spinal cord at several levels by disc protrusions, it appeared probable that this was the cause of the rapid deterioration in his condition. In Case 5, a tabetic, the cervical arthropathy was the cause of severe root pains and muscular wasting in the upper limbs, and the probable cause of his extensor plantar reflexes. In Case 6, a patient suffering from tabes, the cervical arthropathy appeared to be the cause of severe muscular wasting in the upper limbs. In diabetics spinal root lesions, secondary to degenerative changes in the spine, may cause symptoms which, unless the spine is X-rayed, may be attributed to polyneuritis.

Summary

(1) The cervical spine has been X-rayed in 52 cases of syringomyelia.

(2) Significant abnormalities were found in 24, more commonly in males than females.

(3) The incidence of X-ray changes was unrelated to the duration of symptoms.

(4) The X-ray changes were not correlated with the extent of the analgesia, but were correlated with the extent of the lower motor neurone lesions.

(5) There was no correlation between the age distribution of syringomyelics without X-ray changes and that of 100 patients with cervical spondylosis. Syringomyelics with X-ray changes showed an age distribution similar to that of patients with cervical spondylosis.

(6) The X-ray appearances of cervical arthropathy are described.

(7) It is concluded that cervical arthropathy in syringomyelia is due to the same causes as cervical spondylosis, but that the process of degeneration is intensified by the syringomyelia.

(8) Cervical arthropathy in tabes dorsalis and diabetes is described.

(9) The clinical significance of the arthropathy is discussed.

One of us (M. W.) has received a grant for this research from the Empire Rheumatism Council. We are indebted to Dr. Ronald Henson for allowing us to include his patients, and to Dr. M. Jupe for his helpful comments.

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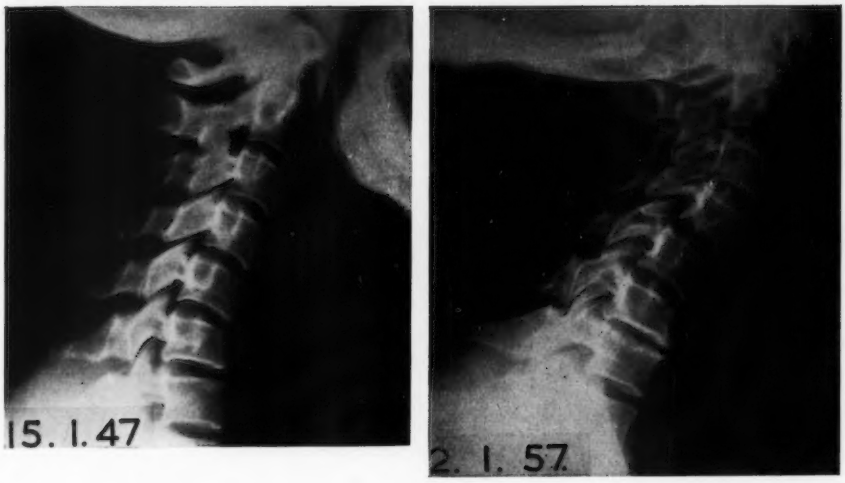
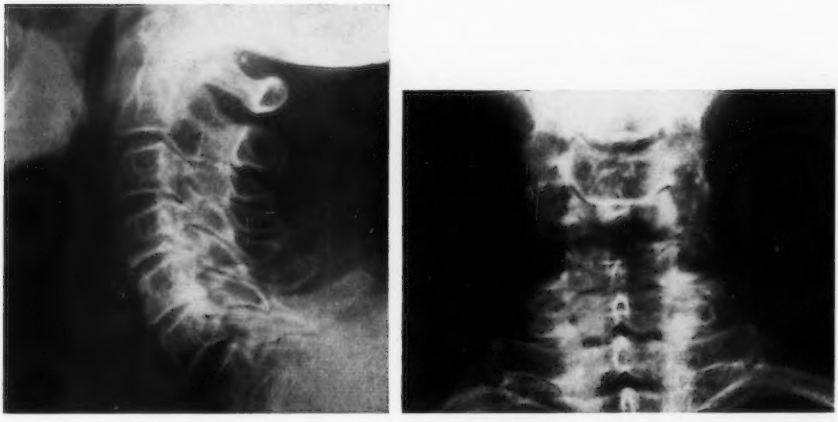


FIGS. 3 and 4.—Changes taking place in the cervical spine of a patient with syringomyelia (Case 1) between 1947 and 1957.



FIGS. 5 and 6.—Syringomyelia (Case 2). Changes somewhat more severe than in Case 1.

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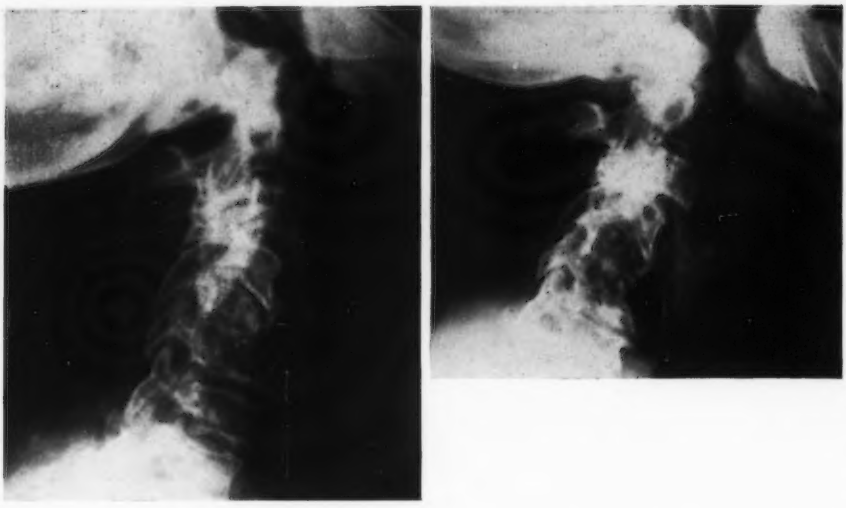
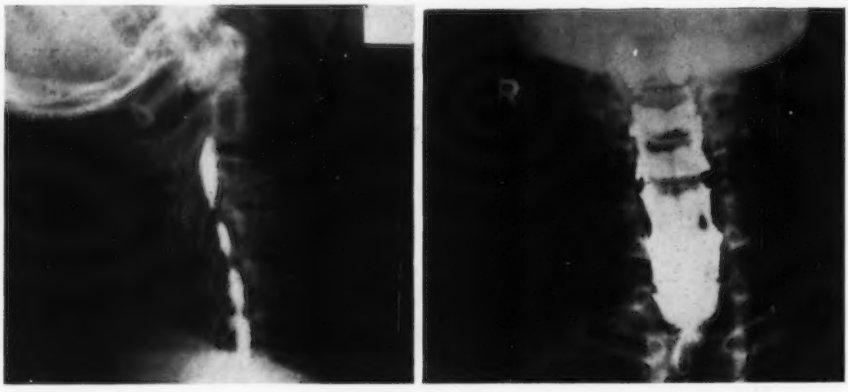


FIGS. 7 and 8.—Syringomyelia (Case 3). Fig. 7 shows the changes fourteen years and fig. 8 twenty years after the onset of symptoms. Cervical laminectomy performed early in the illness probably contributed to the exceptionally severe changes.



FIGS. 9 and 10.—Syringomyelia (Case 4). Myelogram showing disc protrusions in the arthropathic cervical spine. Six years previously the only abnormality was some diminution of the C5–6 disc-space.

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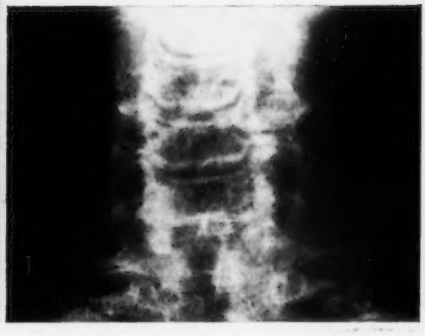
FIGS. 11 and 12.—Tabes dorsalis (Case 5). Arthropathic changes in 1950.



FIGS. 13 and 14.—The same patient in 1954.

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PLATE XXXIV

FIG. 15.

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FIG. 16.

FIGS. 15 and 16.—A severe case of cervical spondylosis showing forward displacement of the body of C3 on C4, gross changes in the bodies of C5, 6 and 7 with severe narrowing of the intervertebral discs and anterior, posterior and lateral osteophytes. The radiological appearances are indistinguishable from those of cervical arthropathy. (Kindly lent by Dr. Graveson.)

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SPINAL MECHANISM OF THE ABDOMINAL AND ERECTOR SPINÆ SKIN REFLEXES[1]

BY

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THE abdominal skin reflex of Rosenbach (1876) has been extensively investigated (*see* Rijnberk, 1937). However, it is still a matter of dispute whether the abdominal skin reflex utilizes a short spinal arc (e.g. Rijnberk, 1937) or a long cerebral arc (Jendrássik, 1894; Marie and Foix, 1912; Monrad-Krohn, 1947, and others). The suggested segmental distribution of the reflex and the occurrence of similar reflexes in patients with complete transverse lesions of the spinal cord (Dejerine and Lévy-Valensi, 1911; Riddoch, 1917) lend support to the supposition that it is a spinal reflex. On the other hand, the intensity of the reflex is intimately correlated to cerebral function and its clinical importance lies in the fact that a pyramidal lesion is usually accompanied by diminution or loss of the reflex on the ipsilateral side, as pointed out by Rosenbach as early as 1876 and by Jendrássik in 1894. These factors have been considered to indicate that the reflex utilizes a long cerebral arc and that its efferent path and even its afferent path (Brodal and Walberg, 1952; Brodal and Kaada, 1953) are associated with the pyramidal tract. Moreover, it has been argued that the abdominal reflexes elicited in patients with spinal transections are pathological substitutes for the normal reflex (e.g. Monrad-Krohn, 1947, 1950).

The abdominal skin reflex has been studied clinically in great detail in order to map out its segmental distribution (Söderbergh, 1923, among others). The reflex was found to be mainly segmental, although the size and spread of the discharge as well as the extent of the receptive field of the reflex vary considerably among normal individuals (*see* Wartenberg, 1945). As regards the function of the reflex, it has generally been assumed that, as its clinical appearance might suggest, it constitutes merely a local contraction of the abdominal wall for the purpose of protecting the viscera against impact. In newborns

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and young infants it has been observed that contraction of the abdominal muscles sometimes is accompanied by contraction of the erector spinæ and an arching of the trunk (Monrad-Krohn, 1918; Lönnum, 1956; Harlem and Lönnum, 1957; and others). It has, however, been questioned whether the abdominal reflexes in infants are identical with those in adults; many authors consider they are not (e.g. Monrad-Krohn, 1950).

In the present study the abdominal skin reflex has been analysed by electromyographic technique in order to determine whether the reflex utilizes a spinal or a cerebral arc and to study in greater detail the reflex patterns evoked by stimulation of the skin of the trunk. The former might be accomplished by proper measurements of latencies and the latter by examining under various experimental conditions the spread of reflex excitations and inhibitions in the abdominal and dorsal muscles.

Some of our results have been briefly reported earlier (Hagbarth and Kugelberg, 1957).

Methods

The great majority of experiments were done on the authors, others were done on medical students and 25 patients in the Neurological Clinic. 5 patients with multiple sclerosis had pyramidal lesions as well as clinically abolished abdominal skin reflexes; the remaining patients had normal reflexes.

The reflexes were elicited with the subject in the recumbent position or sitting on a stool. The skin reflexes were elicited by a rapid stroke with a blunt pin, a tap with a reflex hammer, or, in most instances, by electrical stimulation.

The pin and the reflex hammer were provided with a microswitch connected to an electrical unit. Touching on the skin the microswitch closed the electrical circuit and triggered the cathode ray sweep. The microswitch had a delay of 1–2 msec. The manually applied stroke on the skin was 2–4 in. in length and from 30 to 100 msec. in duration.

The proprioceptive stretch reflex of the abdominal muscles was elicited by a blow with a reflex hammer on a metal ruler pressed firmly against the abdominal wall. In this case the cathode ray sweep was triggered by the contact between the hammer and the ruler.

Electrical stimulation was applied either to the skin or to an intercostal nerve. Two Grass stimulators delivered square wave pulses of about 1 msec. duration and a strength that could be increased to 20 mA. These were applied as single shocks or a series of 2–5 shocks at a frequency of 500/sec. synchronized with the sweep of the oscilloscope. The stimulators could be controlled by a master oscillator which triggered two delay units.

For stimulating the skin two needle electrodes with their tips 4–5 mm. apart were pressed firmly against the skin. For stimulating an intercostal nerve two fine needle electrodes, insulated except for the tips, were inserted 5–7 mm. apart into an intercostal space. Extensive probing was then carried out until excitation of motor nerve fibres, determined by the initial muscle twitch, was obtained at a minimal stimulus strength, usually less than 0·5 mA.

Contraction of the muscles was most often recorded with bipolar needle electrodes. Surface electrodes were used in some experiments but proved less satisfactory. The electrodes were led to one or two condensor-coupled amplifiers and then to a cathode-ray oscilloscope and loudspeaker.

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Results

Features of the Reflex Discharges Evoked by Different Types of Stimulation

A *rapid stroke* with a blunt pin on the skin just below the costal margin evoked an asynchronous reflex discharge in the external oblique (fig. 1 A, Plate XXXVI). The latency of the response to the first stroke was 26 msec. (A1) but increased rapidly with repetition; at the fifth stroke the latency had increased to 38 msec., and at the fifteenth stroke to 46 msec. (A2 and A3).

This lengthening in latency is due to the well-known fact that provocation of the reflex becomes increasingly difficult with repetitive stimulation (cf. Hagbarth and Kugelberg, 1958). Since the reflex is elicited by a spatial and temporal summation of impulses from the skin, the length of the effective stroke must be increased to compensate for the decrease in central excitatory state. Even during a rapid stroke the pin is in contact with the skin for about 50 msec., which obviously permits large variations in latency, the stroke being effective after a variable distance. This factor in part also explains the large individual variations in latency observed, since the briskness of the reflex varies greatly in different individuals. Stroking with a pin, although useful in clinical work, was therefore abandoned.

A *tap* on the skin might be expected to give more reproducible results owing to a less variable spatial and temporal summation. But even this method proved to be unsatisfactory. The reflex latency was found to vary with the velocity of the blow and the compressibility of the tissues. It is, however, well worth noting that a blow with a reflex hammer is capable of evoking the skin reflex (fig. 1 B1). It is commonly believed that a blow on the costal margin or elsewhere on the abdomen evokes only a stretch reflex in the abdominal muscles (Wartenberg, 1945). As shown by Duensing (1940), however, this method of stimulation elicits a skin reflex more often that a stretch reflex. A stronger blow generally evokes both reflexes (fig. 1 B3), but if the skin reflex is weak and the stretch reflex strong, as in spasticity, only the stretch reflex may be evoked. The stretch reflex is distinguished from the skin reflex by its shorter latency and more synchronized volley.

Electrical stimulation of the skin was found to be the most satisfactory method of eliciting the reflexes for analytical purposes. In the following experiments only this kind of skin stimuli was used. Electrical stimulation, if strong enough, is felt like the thrust of a needle into the skin. A single shock was not very effective but a series of 3–5 shocks delivered at the rate of 500 per second generally evoked a reflex response (fig. 1 B2) which had the same appearance as that evoked by natural stimulation. Although not necessarily more effective than a pin stroke, the electrical stimulus is more readily defined and is reproducible in intensity and duration. Earlier workers have employed faradic stimulation of the

skin to elicit the abdominal skin reflex in clinical studies (e.g. Stern-Piper, 1921).

The reflex discharge evoked by a brief stimulus varied greatly in duration and amplitude in different individuals. Maximal current strength of our stimulator evoked in some subjects a very feeble response while in others it evoked a strong response lasting for several seconds. The discharge evoked by a stimulus near threshold strength is more or less asynchronous and lasts from 10 to 40 msec. (fig. 2 B1). If the intensity of the stimulus is increased this discharge may be followed by one or two bursts at a frequency of about 20 per sec. often with complete silence of the motor neurones between the bursts (e.g. fig. 2 A1). The first burst in this series of rhythmic discharges is usually (fig. 2 A1), but not necessarily (fig. 2 B2), the largest and generally it has the lowest threshold. Only occasionally does the second burst appear at a lower stimulus strength than the first. A still stronger stimulus may give rise to one continuous, long-lasting discharge which usually shows a cyclic modulation in amplitude corresponding to the earlier bursts. The skin reflexes of the trunk show the same tendency to a cyclic discharge as the Babinski plantar reflex, the pathological flexion reflex (Kugelberg, 1948), and the normal flexion of the leg (Pedersen, 1954). This phenomenon is not confined to electrical stimulation and may be elicited by a blow with a sharp object.

The cyclic response is not initiated by the abrupt cessation of the stimulus since it occurs with a single shock as well as during continuous stimulation (fig. 2 A2). It must be correlated to events caused by the initiation of the stimulus. If a test reflex (fig. 2 A3, middle record) is interpolated in a rhythmic reflex discharge the former is facilitated during the bursts (not illustrated) and inhibited during the silent periods between the bursts (fig. 2 A3, lower record). Further, if the rhythmic discharge of a skin reflex is obtained against the background of a moderate voluntary or postural contraction the tonic background activity is inhibited between the bursts (fig. 2, lower records in B1 and B2). Thus, a single skin stimulus evokes cyclic facilitation and inhibition of the motoneurones. Inhibition of voluntary activity following the abdominal skin reflex was observed by Duensing (1940) who identified the inhibition with the silent period following a tendon reflex discovered by Hoffmann (1920).

Intercostal nerve stimulation evokes vigorous and widespread reflexes. A strong stimulus (10–20 multiples of the motor nerve fibre threshold) will evoke reflex contractions bilaterally in most of the abdominal wall muscles. The flexors of the hip and also the intercostal muscles and the diaphragm sometimes appear to take part in the contraction as was observed by Downman (1955) in the cat. The far greater efficacy of intercostal nerve stimulation as compared to skin stimulation is explained

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by the larger and more synchronized afferent volley obtained when fibres from a whole segment are stimulated than when receptors and possibly fine nerve branches in a small skin area are stimulated.

The intercostal nerve, however, contains also sensory fibres to the peritoneum and other deep structures which, if stimulated, might add to the imperative nature of the reflex. This seems to be the case especially when the nerve is stimulated behind the axillary line. A strong electrical stimulus here is felt like a knife-stab in the body wall several centimetres in front of the actual site of stimulation. A stimulus applied more ventrally is more often felt like stimulation of a skin nerve and the sensation may be localized entirely to the skin in the ventral part of the dermatome.

The reflex evoked by nerve stimulation is, in latency and appearance, similar to and apparently identical with the skin reflex (fig. 5 C). It is clear that electrical nerve stimulation is a highly unnatural form of stimulation and it has been used mainly for timing the conduction velocity in the peripheral reflex arc. It shows, however, that there are in normal subjects great potential possibilities for a very widespread irradiation of the abdominal skin reflex provided the stimulus is strong enough.

An action potential corresponding to the monosynaptic stretch reflex was inconstantly observed in normal individuals but is more easily detected in spastic patients.

Reflex Pathway

Relationship of reflex latency to stimulus strength.—The larger the response the shorter was its latency (fig. 3 A). A progressive increase of stimulus strength may gradually shorten the latency by as much as 20–30 msec., or 100 per cent. This applies also to intercostal nerve stimulation (fig. 3 B), and accordingly these variations are to be related to variations in the central reflex time, since conduction time in the efferent fibres will be unchanged, and weaker shocks would still affect the faster afferent fibres in the nerve. It is true that a big volley may have a somewhat shorter latency due to a more rapid spread of excitation in the muscle and a more easily detectable beginning of the discharge, but this decrease is negligible compared with that actually found.

Consequently, to estimate the minimal reflex time it is necessary to examine subjects with brisk reflexes and to use strong stimuli which allow for larger responses. Furthermore interferences which alter the briskness of the reflex also tend to alter the latency.

Relationship of reflex latency to irradiation of the reflex.—The shortest latency was found at the segmental level of the stimulus where the contraction was strongest. If the stimulus was applied above the umbilicus near the mid-line the responses of shortest latency could be found within

a restricted area of the rectus abdominis in the immediate vicinity of the stimulating electrode and, within a larger area of the external oblique, just below the costal margin. The distribution of the optimal response has not been systematically studied but the response would seem to be localized to segments in close proximity to the stimulus.

The reflex usually irradiates over several segments both caudally and cranially although not necessarily symmetrically in relation to the stimulus. The latency of the reflex increases with increase in segmental distance from the point of stimulation. The lengthening of latency is generally not gradual; it tends to occur in a jump of about 20 msec. as the recording electrodes are gradually moved cranially or caudally from the area of optimal response. For this reason a discharge in the periphery of the irradiation zone often coincides with the period of inhibition following the optimal response (fig. 4 A and B). Indeed, if the two responses are rhythmical, the repetitive bursts may alternate in the respective areas. If the distant response is examined against the background of a tonic discharge it is often seen to be preceded by an inhibition coinciding with or slightly succeeding the optimal response (fig. 4 B2). This inhibition was weaker and shorter than the inhibition following a reflex discharge and its exact time of onset was difficult to determine. The relation in time between this inhibition and the optimal response has therefore not been sufficiently well determined to allow any definite conclusions about its nature. It could possibly be explained on the basis of an external loop, the phenomenon being the result of the muscle contraction accompanying the optimal discharge rather than events primarily occurring in the reflex centre.

It is striking to observe how rhythmic discharges within two portions of the same muscle may be out of phase. Even though the underlying mechanism is obscure the responses may be said to behave in an antagonistic fashion. The physiological significance of the fact that each abdominal discharge tends to be surrounded by inhibition, temporally as well as spatially is unclear.

Conduction velocity in the afferent and efferent nerve fibres.—The afferent velocity was measured in one subject with very brisk reflexes, and in 5 subjects with moderately high reflex thresholds. Stimulation was applied to the skin near the mid-line and to the corresponding intercostal nerve at a given distance from the skin electrode. In the subject with a low reflex threshold (fig. 5 B) the difference in latency was 5·5 msec. with a distance of 22 cm. between the skin and nerve electrodes. This corresponds to an afferent conduction velocity of 40 m.p.s. In the subjects with higher reflex threshold (fig. 5 C) the afferent conduction velocity varied from 20 to 30 m.p.s. Evidently the afferent fibres mediating the abdominal skin reflex have a broad calibre spectrum. Only in relatively few individuals can a reflex be provoked by innocuous

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or practically innocuous stimulation of low threshold nerve fibres. Stronger stimuli which also affect smaller fibres more regularly evoke a reflex.

The variation in afferent conduction velocity is yet another factor which contributes to the latency variations of the abdominal skin reflexes. It explains to some extent the longer latency found when the skin reflex is not easily elicitable.

The efferent conduction velocity as measured by stimulation of an intercostal nerve at two different points and recording the difference in the latency of the direct muscular response was found to be 55 m.p.s.

Central delay.—The latency of the reflex has been shown to vary over a wide range according to the method of stimulation, the stimulus intensity in relation to the central excitatory state, the point of recording in relation to the site of stimulus, and variations in afferent conduction velocity. This may explain the discrepancies between various observers on this point; Hertzog (1918) reported a latency of 80–130 msec., Guillain *et al.* (1924) 100 msec., Lehner (1941) 60–90 msec. and Duensing (1940) with electrical skin stimulation, 35–50 msec.

The shortest latency found in an adult subject, measured from the beginning of the stimulus, was 24 msec. (fig. 5 A). The stimulus consisted of 3 repetitive shocks at intervals of 2 msec. Since the latency of the response to a single shock was 26 msec. and diminished to 24 msec. when two or more shocks were applied, the minimal latency should have been at least a further 2 msec. shorter, the second stimulus being the effective one. In this subject the afferent reflex arc was 45 cm. and the efferent 39·5 cm. With an afferent conduction velocity of 40 m.p.s. and an efferent conduction velocity of 55 m.p.s. the central delay is 3·55 msec. In the subject represented in fig. 5 B the central delay was 5·4 msec. if a similar correction of reflex time is made. A central delay of 3·55 to 5·4 msec. allows for a spinal multisynaptic reflex but excludes the possibility of a cerebral reflex arc which would about double the length of the reflex arc, i.e. an increase of 80 or 100 cm. measured over the brain-stem and cortex, respectively.

The conclusion that the abdominal skin reflex is a spinal polysynaptic reflex is supported by a comparison with the monosynaptic stretch reflex which in these subjects had a latency of 18 msec. The difference in latency of 4·5 msec. is well explained by a few more synapses in the reflex centre and the slower conduction velocity in the afferent arc.

Interaction of Abdominal and Erector Spinæ Skin Reflexes

In normal individuals with brisk abdominal reflexes it was often seen that a stimulus applied to the abdominal skin near the mid-line evoked bilateral responses in the rectus abdominis and the external oblique (fig. 6 A). The reflexes were always stronger on the side stimulated,

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resulting in a deviation of the umbilicus toward the ipsilateral side. If the abdominal skin stimulus was applied during steady voluntary contraction of the erector spinæ muscles the activity in these muscles is inhibited during the abdominal reflex discharges. Thus, the abdominal skin reflex produces not only a contraction of the abdominal wall muscles but also a reciprocal inhibition of the antagonistic dorsal muscles. This tends to bend the body forward, retracting the abdomen from the noxious stimulus. If the stimulus is strong and the reflex is brisk a forward bending of the trunk is actually observed.

A progressive shift of the stimulus laterally within one and the same dermatome gradually changes the reflex pattern. For example, when the stimulus is applied at the lateral border of the trunk the maximal abdominal response has shifted laterally. The maximal inhibition appears in the contralateral erector spinæ and external oblique (fig. 6 B). This tends to bend the body toward the side stimulated.

A stimulus applied farther back at a point about 10 cm. from the spine evokes a weak reflex contraction of the ipsilateral external oblique and evokes a strong reflex contraction of the ipsilateral erector spinæ (cf. Foerster, 1936). The reciprocal inhibition is seen in both recti abdominis and in the contralateral external oblique and erector spinæ (fig. 6 C). This reflex pattern tends to bend the trunk backwards toward the side stimulated.

A shift of the stimulus a few centimetres nearer the spine is sufficient to change the reflex pattern again. If the stimulus is applied to the dorsal mid-line the erector spinæ reflex response is bilateral and symmetrical (fig. 6 D). The body now tends to bend straight backwards, retracting the spine from the stimulus.

It appears that each skin-point is functionally associated with an appropriate reflex-withdrawal pattern. Fig. 7 illustrates how a conflict arises when stimuli are applied simultaneously to opposite sides of the trunk. The skin stimulus over the erector spinæ evokes by itself a very strong reflex (fig. 7, 1, lower record) and the stimulus over the rectus abdominis a weaker reflex contraction (fig. 7, 2, upper record). If both stimuli are applied simultaneously the erector spinæ reflex is to a large extent suppressed (fig. 7, 3, lower record) and the abdominal reflex is abolished (upper record). The issue of the competition between the rival reflexes is largely dependent on the relative intensities of the stimuli, the inherent strength of the respective reflexes and, probably, the posture of the trunk.

Influence of contraction.—A weak sustained contraction of the muscle increases the intensity of the reflex response as shown in fig. 8 B. This is in accordance with the observations of Wartenberg (1945). The increase in the size of the reflex runs parallel with a shortening of its latency which may be as much as 20 msec. or more (fig. 8 B2).

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A stronger contraction does not necessarily further augment the size of the reflex response. The erector spinæ skin reflex evoked at rest (fig. 8 A2) is but little increased by a moderate voluntary contraction (fig. 8 A3). Actually, the reflex discharge is swamped by the voluntary discharge and is difficult to detect. It is probable that a large number of the motor neurones which ordinarily are reflexly activated had already been brought into action by the voluntary contraction. The inhibition following the discharge is, however, very marked and appears at a somewhat shorter latency than would be expected from the reflex discharge at rest.

A contraction of the antagonist, on the other hand, suppresses the reflex response and increases the latency, as shown in the erector spinæ reflex evoked during contraction of the rectus abdominis (fig. 8 A1).

Thus, it is clear that contractions strongly affect the latency and size of the skin reflexes of the trunk. But does contraction alter the reflex patterns? Some of our experiments would seem to show that it does. For instance, in the subject represented in fig. 8 C, a strong skin stimulus applied at the lateral border of the trunk evoked a vigorous response in the ipsilateral (C1 upper record), and a weak response in the contralateral external obliques (C1 lower record). If the subject now contracted his contralateral external oblique, the reflex response in this muscle was replaced by inhibition (C2 lower record). So far as the contralateral external oblique is concerned the reflex pattern is profoundly altered by a change in posture. The muscles which in the reflex pattern at rest behaved as agonists now behave as antagonists.

The opposite effect has also been observed. For example, a stimulus over the rectus abdominis during contraction of the erector spinæ evoked a scarcely discernible abdominal reflex (D1 upper record). This feeble abdominal reflex was, however, accompanied by a very marked reciprocal inhibition of the erector spinæ corresponding in time to the abdominal reflex and followed by a rebound (D1 lower record). As expected the rectus abdominis reflex is much larger and better seen when evoked during moderate contraction of the muscle and the reflex was now followed by the usual silent period (D2 upper record). During strong simultaneous contractions of both the abdominal and erector spinæ muscles the abdominal reflex was less clearly observed, but the inhibition was unchanged, and had the same latency (D3 upper record). In the erector spinæ, however, the inhibition had shifted to the right and coincided in time with the inhibition of the rectus abdominis (D3 lower record). The muscles now behave as synergists.

The two last-mentioned experiments were not easily reproducible. The site of the stimulus and the contraction pattern which induces a reversal of the reflex would seem to be rather critical.

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Abdominal Skin Reflexes in Spasticity

Five patients with spasticity due to disseminated sclerosis were investigated. All had clinically abolished abdominal skin reflexes. Electrical single shock stimulation of an intercostal nerve, however, evoked in all the patients a reflex similar to the abdominal skin reflex (fig. 9 A and B). The conduction velocity of the afferent fibres mediating the reflex was estimated by stimulating the intercostal nerve at three points, 8·5, 14·5 and 21 cm., respectively, from the point of recording. Between the first two points the conduction velocity was 7·8 m.p.s. and between the last two points 9·3 m.p.s. Care was taken to adjust the stimuli so that all responses were of equal size.

Discussion

The afferent fibres conveying the abdominal skin reflex have a broad calibre spectrum. In subjects with brisk abdominal reflexes mediation may occur in fibres with a conduction velocity of 40 m.p.s. but in most subjects the reflexes require activation of fibres with a conduction velocity of 20–30 m.p.s. In patients with disseminated sclerosis and clinically abolished abdominal reflexes activation of fibres with a conduction velocity of 9 m.p.s. was adequate to evoke a reflex similar to the abdominal skin reflex. These facts may merely reflect the necessity to activate more and more fibres as the central threshold is raised, but it is also probable that the modality of the stimulus plays a significant role. A large proportion of the fibres with a conduction velocity of about 20 m.p.s. mediate pain (e.g. Gasser, 1943) and noxious skin stimuli are much more potent than innocuous ones.

Although the abdominal skin reflex may be regarded as a nociceptive reflex, in the sense given by Sherrington, it is worthy of note that the reflex may be elicited by stimuli of innocuous quality, such as touch. It is obvious, however, that our defence reactions must be attuned to their biological function. While most individuals react to a sudden touch on the face with a blink reflex to protect the delicate eye (e.g. Kugelberg, 1952), the abdominal viscera do not need such a sensitive defence mechanism, and the back still less so. In fact, relatively few subjects respond with a reflex to a touch on the abdomen. The erector spinæ skin reflex has a still higher threshold; and is often absent among normal individuals even on moderately painful stimuli.

If "pain" compared with "touch" is just a matter of more or less intense stimulation of identical sensory units, it is not surprising that "touch" may be an adequate stimulus for a nociceptive reflex. But since probably the two modalities to some extent are correlated with separate sets of sensory units, it might be questioned why a touch stimulus should ever evoke a nociceptive withdrawal reaction. There seems to be a plausible answer to this question. The fastest route from skin to spinal

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cord primarily mediates touch impulses and there would be a considerable gain in speed if this route were employed. The fastest fibres which we have found capable of eliciting the reflex may exclusively subserve signals from touch receptors, which do not tell us whether a stimulus is noxious or not. But an abdominal defence mechanism triggered by touch impulses would certainly be rather embarrassing if it were not intelligently controlled. Indeed, as will be shown in a subsequent paper (Hagbarth and Kugelberg, 1958) the trunk skin reflexes are centrally governed, permitting appropriate responses for each situation.

It has been shown that the abdominal skin reflex is a spinal polysynaptic reflex. Under optimal conditions the central delay is comparable to that given for spinal multisynaptic reflexes in the cat: 3·5–5·5 msec. for the flexion reflex of the hind-limb (i.e. Creed, Denny-Brown, Eccles, Liddell and Sherrington, 1932), and 2·4–2·8 msec. for reflexes evoked by stimulation of an intercostal nerve (Downman, 1955). To be quite accurate, it is usually only the initial deflection of the asynchronous Emg-response which has a latency short enough to exclude a long cerebral reflex arc. Spinal polysynaptic skin reflexes, however, are known to cause asynchronous discharges and therefore there is little reason to suspect that the later deflections of the Emg-response are due to anything else but temporal dispersion of impulses in the periphery and in the spinal cord. It is also true that long latencies which do not exclude the possibility of a cerebral arc are often found on weak stimuli as well as in regions outside the optimal area. Stronger stimuli, however, gradually shorten the latency until a cerebral arc is excluded. Furthermore there is little reason to believe that the responses in non-optimal areas are not of the same nature as the short latency response in the optimal area. Very late responses of voluntary origin are, however, often seen.

The rhythmic discharges of the trunk skin reflexes have a strong resemblance to those obtained by Bernhard and Therman (1947*a*, *b*) in the cat, and by Hoffmann, Schenck and Tönnies (1948) and Schenck and Koehler (1949, 1950) in man. These authors stimulated various skin nerves in the limbs and obtained a cyclic facilitation and inhibition of the motor neurones of a rhythm comparable to ours (*see also* Hagbarth, 1952). They interpreted the phenomenon as arising primarily in the reflex centre.

On the other hand, it is well known that the excitability of the motor neurones is strongly influenced by the proprioceptive inflow from the muscle (e.g. Matthews, 1933; Granit, 1950). A prolonged reflex discharge might well be inhibited temporarily by a muscle contraction set up by the reflex. If this cycle is repeated several times a rhythmic discharge of the skin reflex might possibly ensue. In that case the mechanism underlying the rhythmicity might be the same as for the silent period after the tendon reflex (Granit, 1950; Merton, 1951). The mechanism responsible for the rhythmicity of the trunk skin reflexes is still obscure. We have searched for cyclic facilitation and inhibition following stimuli too weak to elicit

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a reflex contraction. There was no evidence of inhibition, a fact which points in favour of the muscle contraction as the underlying cause. But the threshold of the trunk skin reflexes is so unstable that it is very difficult to obtain conclusive results in experiments of this type. The fact that the second burst may occasionally be evoked at a lower threshold than the first burst would point to rhythmicity without interference of muscle contraction. However, it is difficult to exclude the possibility that an earlier burst and a very feeble muscle contraction may have occurred in near-by regions of the muscle but were not recorded.

The abdominal skin reflexes have been described as a series of unisegmental reflexes (Rijnberk, 1937). It may be misleading, however, to lay too much stress on the segmental organization. Our electromyographical recordings show little evidence of any strict segmental boundaries. The reflex irradiates over several segments ipsilaterally and, to a less extent, contralaterally. However, the most open reflex path between skin and muscle is confined to the segment in the vicinity of the root of entrance.

Both the abdominal and the erector spinæ skin reflexes were found to represent a much more elaborate defence mechanism than has generally been assumed. The reflex pattern of contractions and reciprocal inhibitions gradually changes as the stimulus is moved transversely across the trunk within one and the same dermatome, and in critical areas a shift of the stimulus of only a few centimetres is sufficient to produce a clearly detectable change in the reflex pattern. At whatever point on the circumference of the trunk the stimulus is applied it produces a specific pattern, which tends to induce a movement away from the stimulus, as well as a contraction of adjacent muscles for protection of underlying tissues. It appears that a large number of allied abdominal and erector spinæ skin reflexes are harmoniously knit together in a single mechanism for the protection of the trunk. It is likely that other protective skin reflexes in man are organized in essentially the same way as the trunk reflexes. This view is supported by preliminary experiments on the lower limbs (Hagbarth, in the leg, and Kugelberg, in the foot).

The almost compass-like withdrawal of the trunk skin reflexes has so far not been encountered in other protection reflexes. A withdrawal in two opposite directions according to the point stimulated was, however, observed by Sherrington (1906) in the cat's tail. Recently Hagbarth, (1952) has found that each of the flexor muscles of the cat's leg were excited from most parts of the limb but inhibited from a skin area mainly localized over the antagonistic extensor muscle. Stimulation of the skin covering an extensor muscle on the contrary elicited contraction of this muscle and reciprocal inhibition of its antagonist.

The reflex evoked by a given stimulus is not invariably the same, and may be altered by a change in posture or by an appropriate voluntary contraction. Such changes were found greatly to affect the

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latency and size of the reflex discharge but occasionally also to induce a reversal of the reflex effect. Reversal is generally considered to be indicative of concealed reflexes (Creed *et al.*, 1932). The fact that the reflex pattern changes gradually from one near-by point to another so that converse reactions are initiated at two distant points indicates that at each point the reflex actually is the result of an interaction of conflicting reflexes. It seems as though this balance, at least on stimulation of certain critical areas, could be radically overthrown by, e.g., a change in posture. The functional significance of this requires further study.

A striking feature of the trunk skin reflexes is the fact that the inhibitions are as prominent as the contractions. We have not studied the reflexes evoked by prolonged stimulation owing to the difficulty of distinguishing a reflex response from other types of contractions when latency control cannot be used. Continuous stimulation would otherwise better reproduce many pathological conditions, such as abdominal rigidity and spasms of the erector spinæ due to meningeal irritation, sciatica, and so on. It is, however, probable that reciprocal inhibition plays an important role in the postural abnormalities assumed as the result of persistent pain in abdominal and spinal structures.

Summary

The abdominal and erector spinæ skin reflexes have been investigated in 35 subjects with electromyographical technique. The reflexes were elicited by mechanical stimulation of the skin or by repetitive electrical shock stimulation of the skin or an intercostal nerve.

(1) The conduction velocity in the afferent arc was found to be as high as 40 m.p.s. provided the reflex threshold was low. At higher reflex thresholds the afferent conduction velocity was 20–30 m.p.s., apparently due to the necessity of activating finer, more effective nociceptive fibres.

(2) The abdominal skin reflex is a spinal polysynaptic reflex with a minimal central delay (3·55–5·4 msec.) comparable to that reported for spinal polysynaptic reflexes in experimental animals. The loss of the reflex in pyramidal lesions is consequently due not to the interruption of a hypothetical cerebral reflex arc but to a diminished excitability of the spinal reflex centre.

In 5 patients with disseminated sclerosis and clinically abolished abdominal skin reflexes shock stimulation of an intercostal nerve still evoked a reflex response similar to the abdominal skin reflex.

(3) The trunk skin reflexes following shock stimulation may show a series of rhythmic bursts at a frequency of about 20 per sec. often with complete silence of the motor neurones between the discharges. A tonic background activity as well as an interpolated skin reflex discharge is inhibited between and facilitated during the rhythmic bursts.

(4) The abdominal skin reflexes show little evidence of any segmental boundaries and irradiate over several segments ipsilaterally, and, to a less extent, contralaterally. The shortest latency response is confined to segments in the immediate vicinity of the stimulus. In distant segments the latency is increased so that the response usually coincides in time with the period of inhibition of the optimal response; if the responses are rhythmical they may alternate in the respective areas. Even though the underlying mechanism is obscure the responses may be said to behave in an antagonistic fashion.

(5) The skin reflexes of the trunk, of which the abdominal reflex is but one, form an elaborate defence mechanism with a specific pattern of contractions and reciprocal inhibitions according to the skin area stimulated. At whichever point on the circumference of the trunk the stimulus is applied it results in a reflex pattern which tends to induce a movement away from the stimulus as well as a contraction of adjacent muscles for protection of underlying tissues.

Consequently, reflexes evoked by simultaneous stimulation at two opposite points of the trunk were found to inhibit one another due to conflicting effects.

(6) The trunk skin reflexes are generally facilitated by a weak or moderately strong contraction of the muscle activated and inhibited by a contraction of its antagonist. This affects not only the size of the reflex but also to a large extent its latency.

Postural and voluntary contractions may profoundly alter the reflex pattern and may cause a reversal. A reflex contraction has been observed to be changed to inhibition and vice versa.

(7) A striking feature of the trunk skin reflexes is the fact that various types of inhibition are as prominent as contractions. It is inferred that reciprocal inhibition plays an important role in the postural abnormalities assumed as the result of persistent pain in abdominal and spinal structures.

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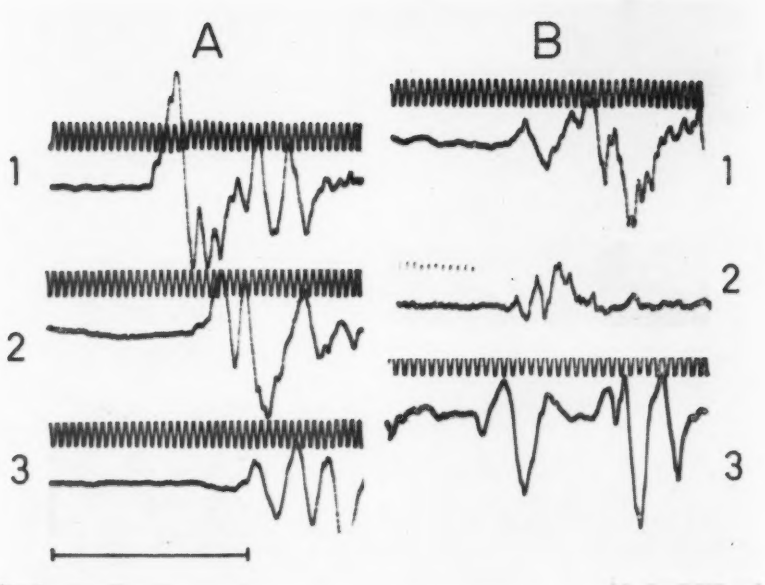

FIG. 1.—Abdominal reflexes evoked by different types of skin stimulation A, Stroke with blunt pin. A1, following the first stroke; A2, following fifth stroke; A3, following fifteenth stroke, showing increase in latency on repetitive stimulation. The same reflex evoked by: B1, a blow with a reflex hammer; B2, electrical stimulation, B3 (another subject), a strong blow, evokes a stretch reflex which precedes the skin reflex. (Recorded with surface electrodes.) Time markers (2 msec.) in this and all subsequent figures, except fig. 2, A2.

To illustrate article by E. Kugelberg and K. E. Hagbarth.

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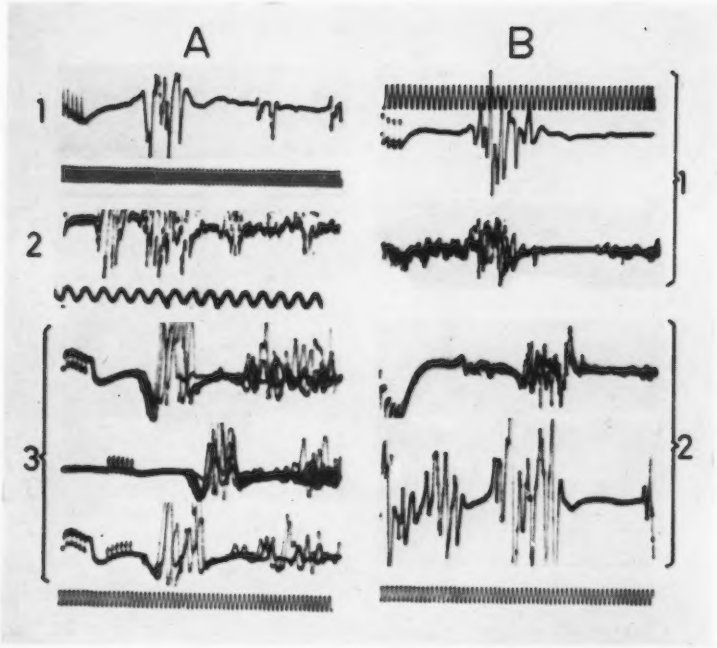

FIG. 2.—Cyclic reflex discharge evoked by A1, brief electrical stimulus and A2, continuous stimulation (Time: 20 msec.), A3, upper record, a cyclic skin reflex discharge. Middle record, a test reflex. Lower record, shows inhibition of test reflex when interpolated in the period between the two bursts of the unconditioned reflex. B1, reflex response in the external oblique (upper tracing) and its influence on steady voluntary contraction (lower tracing), showing a silent period after the reflex discharge. B2, same, with cyclic reflex response, in rectus abdominis.

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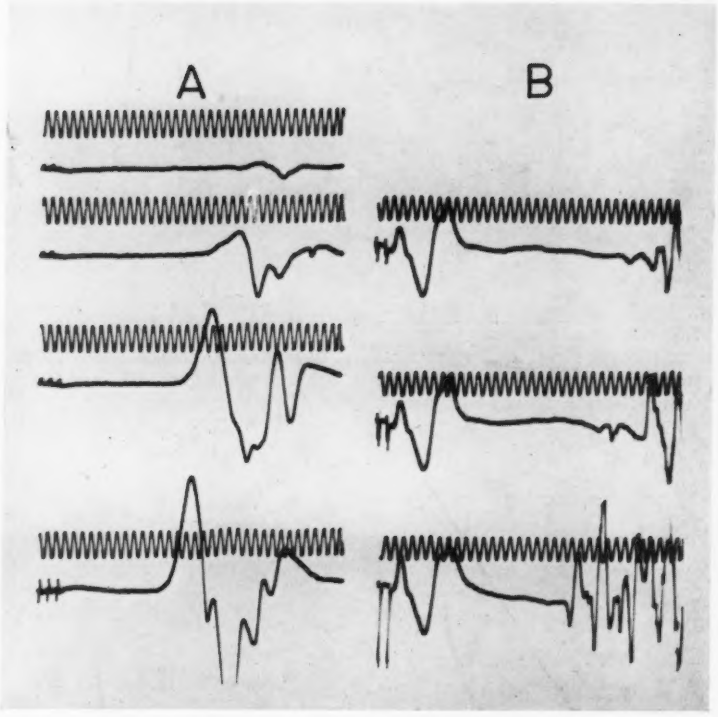

FIG. 3.—A, electrical skin stimulation, and B, intercostal nerve stimulation, showing a progressive decrease in latency and increase in size of reflex response with increasing stimulus strengths.

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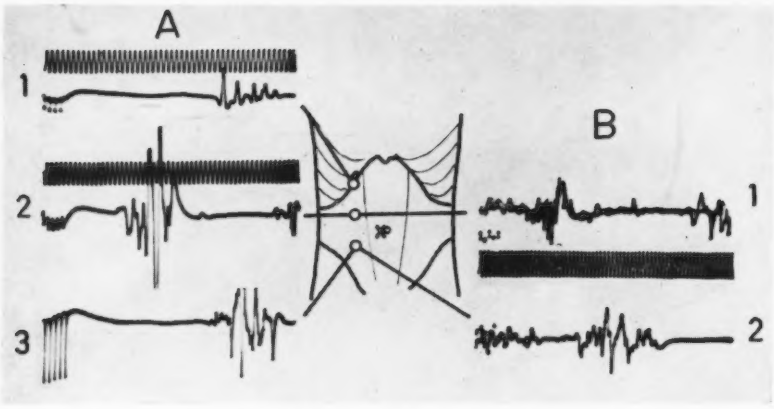

FIG. 4.—Reflex latency in relation to site of recording. A2, optimal area. A1 and A3, cranial and caudal segments. The reflex responses at distant segments alternate with the bursts in the optimal area. B, reflex evoked against the background of a steady contraction. The reflex response in the optimal area (B1) coincides with inhibition of steady activity in caudal segment (B2), and vice versa.

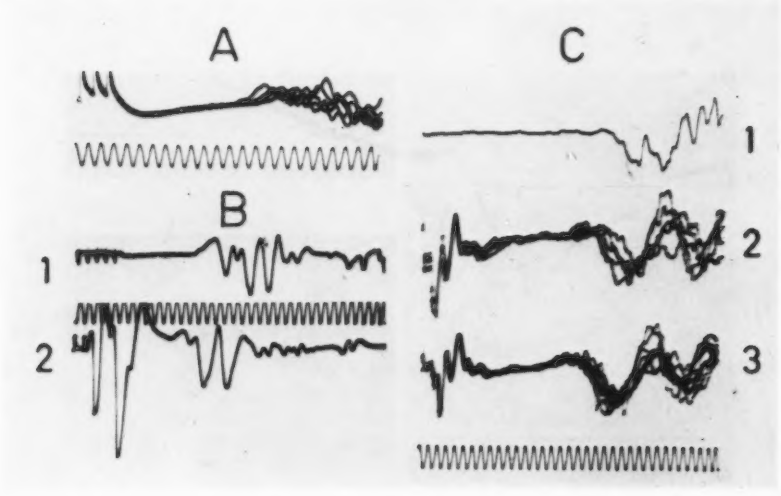

FIG. 5.—A, shortest reflex latency; 5 superimposed records. B, another subject. B1, reflex response to electrical skin stimulation near the mid-line and B2, intercostal nerve stimulation 22 cm. lateral to the stimulus in B1, showing a decrease in reflex time of 5·5 msec. C, another subject. C1, reflex evoked by stroke with blunt pin near mid-line. C2 and C3, intercostal nerve stimulation with a distance of 9 cm. between stimulating electrodes; 6 superimposed records. (Recorded with surface electrodes.)

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PLATE XL

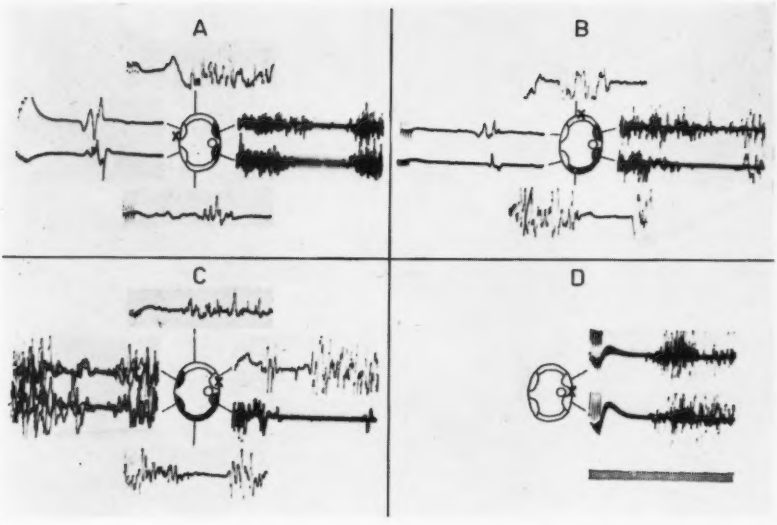

FIG. 6.—Reflex patterns obtained by skin stimuli applied to various points marked by x along the circumference of the trunk within one and the same dermatome. The filled-in muscles indicate contraction, the reflex being evoked against the background of a steady discharge. Full description in text.

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PLATE XLI

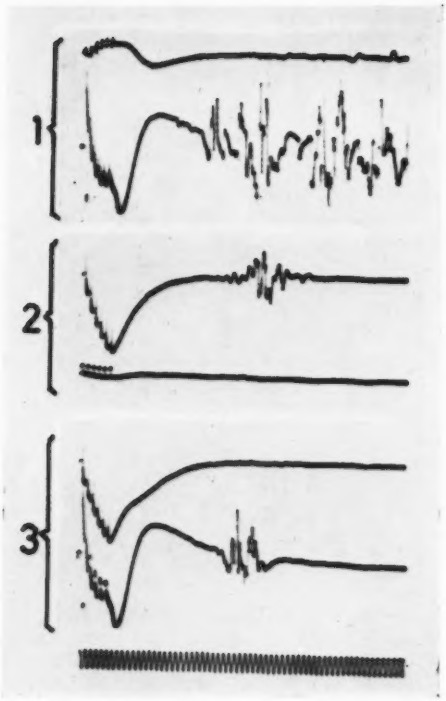

FIG. 7.—1, a skin stimulus over the erector spinæ muscle evokes a strong reflex response in the muscle (lower tracing). 2, a skin stimulus over the rectus abdominis evokes a moderately weak response in this muscle (upper tracing). 3, simultaneous stimulation at points 1 and 2 diminishes the erector spinæ reflex and inhibits the rectus abdominis reflex.

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PLATE XLII

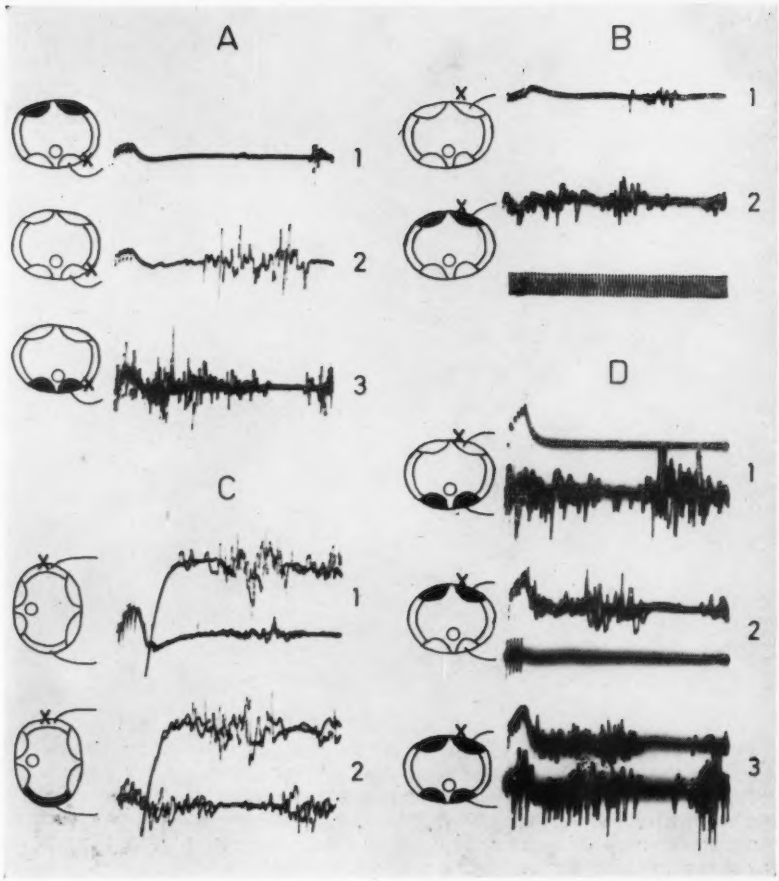

FIG. 8.—Influence of contraction on the skin reflexes. Point of stimulation marked by x. Filled in muscles indicate contraction. A represents the erector spinæ and B the rectus abdominis reflexes. Contraction of the antagonist (A1) suppresses the reflex as compared with the reflex evoked at rest (A2). Contraction of the muscle activated (B2), facilitates the reflex. C and D show reversal of reflex effects. Full description in text.

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PLATE XLIII

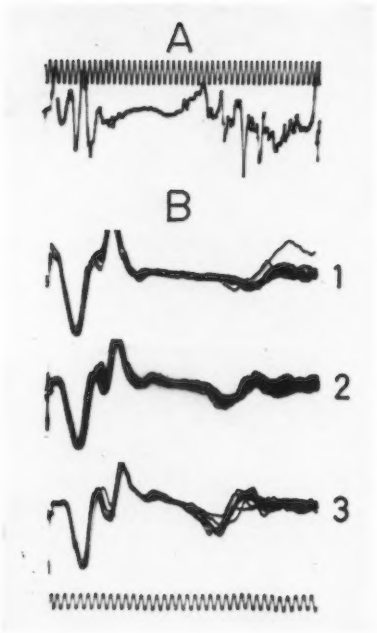

FIG. 9.—Intercostal nerve stimulation in two patients with disseminated sclerosis, A and B, with clinical abolished abdominal skin reflexes showing a polysynaptic reflex discharge similar to the abdominal skin reflex discharge. In B1, 2 and 3 stimulating electrodes are 8·5, 14·4 and 21 cm. resp. lateral to the recording electrode, showing diminution in latency as the stimulating electrode is moved nearer the spinal cord. In each record 5 traces superimposed.

To illustrate article by E. Kugelberg and K. E. Hagbarth.

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PLASTICITY OF THE HUMAN ABDOMINAL SKIN REFLEX[1]

BY

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IN a previous study the human abdominal skin reflex was analysed by electromyographic technique and its central latency was found short enough to prove that the reflex is mediated by a spinal reflex arc (Kugelberg and Hagbarth, 1958). It was demonstrated that in addition to contraction of the abdominal muscles there is also a reciprocal relaxation of the trunk erector muscles and the "local sign" of the reflex is such that the ensuing movement causes withdrawal from the stimulus. The abdominal reflex was found to be but one manifestation of an elaborate spinal defence mechanism which functionally connects each skin area of the trunk with the appropriate withdrawal and protecting muscles.

It has long been known that normally the behaviour of the abdominal skin reflex is correlated to cerebral functions (Jendrassik, 1894) and it is a well-known clinical fact that suprasegmental lesions may affect the strength of the reflex (for ref. *see* van Rijnberk, 1937). In view of the evidence for the spinal nature of the reflex, this cerebral interference is of special interest. Our basic knowledge of spinal withdrawal reactions is derived from experiments on spinal, decerebrate or anæsthetized animals. These fundamental studies allow an accurate analysis of the spinal mechanisms involved, but they are not likely to reveal how spinal function may be integrated with the normal function of higher centres. The abdominal skin reflex offers an opportunity of studying how a spinal withdrawal reaction behaves in the intact organism where the spinal reflex centre is subjected to the influence of the normal functioning brain.

In the present study it is shown that the abdominal skin reflex has plastic properties which cannot be accounted for by spinal function alone. In many respects the reflex behaves like a conditioned reaction for which a painful abdominal stimulus constitutes the unconditioned stimulus. By training procedures the reflex can be extinguished or enhanced for long

[1]Acknowledgment: This paper was facilitated by a grant from the Swedish Medical Research Council.

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periods of time and it can be trained to respond selectively to certain kinds of abdominal stimuli. The strength of the reflex can be changed also by verbal suggestion or by any procedure which is liable to influence the subject's expectancy of abdominal pain.

It is concluded that the adaptability of the reflex is due to a cerebral outflow which selectively adjusts the excitability of the spinal interneurones mediating the reflex. The results are discussed in relation to the theories of conditioning and their clinical relevance is evaluated (cf. preliminary report by Hagbarth and Kugelberg, 1957).

Methods

The experiments were performed either on ourselves or on patients from the neurological clinic, all of them having normal abdominal reflexes. Only adult subjects were chosen, usually young men.

In the experiments care was taken not only to control the way in which the abdominal stimuli were presented but also to exclude extraneous stimuli that might interfere with the responses. Usually the subject lay comfortably supine with his eyes closed and with plugs in his ears. He had been told to relax and not to pay undue attention to the abdominal stimuli, which were given without warning as to quality or location (unless otherwise stated). In the experiment illustrated in fig. 2, Plate XLV, the subject was sitting.

For the present purpose it was essential to use stimuli that with a fair amount of accuracy could be easily reproduced. Therefore, electrical stimulation or mechanical tapping of the skin was preferred to the more common stroking technique. The taps were applied with a blunt object, either manually or by a lever with adjustable weight and falling distance. In spastic subjects the tapping can evoke a stretch reflex but normally this short latency response requires a more massive stretching of the muscles (cf. Duensing, 1940; Kugelberg and Hagbarth, 1958). Hard abdominal blows were always applied manually. The sweep of the cathode-ray oscilloscope could be triggered by way of a microswitch attached to the blunt object. Bipolar needle electrodes were regularly used for recording. For further description of stimulation and recording technique *see* Kugelberg and Hagbarth, 1958.

Results

Lowering of excitability by repetition (*habituation*).—The stimulus threshold of the abdominal skin reflex is subject to great individual and incidental variations. Sometimes painful stimuli are required while in other instances any kind of weak skin stimuli may be effective. In an initial series of experiments the reflexes were elicited by weak, non-painful abdominal skin stimuli. It was regularly observed that repetition of such a stimulus caused a gradual diminution of its efficiency until eventually the response was completely extinguished. Previous workers have regarded this property of the abdominal skin reflex as a manifestation of inhibitory processes in the central nervous system (cf. Wichtl, 1935) and the phenomenon has been referred to as habituation (Lehner, 1941). The present study confirms that the gradual decline of the abdominal reflex response has those characteristics which are usually included in the term habituation (Hilgard and Marquis, 1940).

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Usually the rate of repetition was 5–10 per min. but decrement of response was also observed with longer intervals between successive stimuli. During the course of repetition the response was diminished as shown by the amplitude of the muscular discharge at the site of the recording electrode, which had usually been placed in that part of the abdominal wall where the contraction appeared to be strongest. As the amplitude of the response diminished there was also a gradual reduction of the spatial distribution of the muscular contraction in the abdominal wall. Before the response was totally abolished only a small and circumscribed contraction could be seen in the immediate vicinity of the recording electrode.

In regard to the number of stimuli required to abolish the response the individual variations were very great. In subjects exposed to the procedure for the first time the response could be extinguished by less than 10 stimuli or it could remain after more than 100 repetitions. Stimulation at a faster rate (once every 2 or 3 seconds) made the response decline more rapidly than when stimulation intervals were 10–15 sec.

An interruption of the stimulus sequence tended to cause a recovery of the response. Once the habituation was complete, in the sense that a number of consecutive stimuli elicited no responses, a short rest from stimulation could give rise to a complete restoration of the response, although at times the unresponsiveness persisted after a pause of several minutes.

When the reflex was allowed to recover between series of stimulation sequences, the cumulative effect of habituation was noted (cf. Lehner, 1941); a smaller number of stimuli are required to abolish the response if the subject has previously been exposed to similar habituation procedures. This cumulative effect of habituation could sometimes be demonstrated even if hours elapsed between successive series of stimulation.

As Lehner points out, at times extraneous stimuli or any sudden change in the total experimental situation cause a sudden restoration of habituated abdominal reflex. This kind of restoration (or disinhibition) was not an easily reproducible phenomenon. It must be emphasized, however, that the rapid recovery that sometimes follows a rest from stimulation might be classified as a similar phenomenon in the sense that the temporary absence of stimuli constitutes a change in the total experimental situation.

The question arises as to what link of the spinal reflex arc is affected by the habituation. Is it the motoneurone excitability that is lowered or does the blocking occur internuncially so that the afferent impulses are prevented from reaching the final common pathway? The experiment illustrated in fig. 1 seems to give a reliable answer to this question. In this experiment two pairs of stimulating electrodes were attached 4–5 cm. apart on the abdominal skin surface and weak electrical stimuli were delivered alternatively to one pair of electrodes (*stim. A*) or the other

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(*stim. B*). Initially, *stim. A* and *B* were equivalent in the sense that they evoked abdominal contractions of similar magnitude within the same portion of the abdominal musculature (*see* first two records). When, after 29 repetitions of *stim. A*, the response had been completely abolished, *stim. B* was substituted without interrupting the sequence of stimulation. Apparently the habituation to *stim. A* had not diminished the effectiveness of *stim. B*, which had to be repeated several times before the response was again extinguished. Then, a sudden return to *stim. A* showed that in the interim this stimulus had partly regained its effect. As the experiment went on with sudden exchanges of stimuli it became increasingly clear that the process of habituation discriminates between *stim. A* and *B* so that it selectively suppresses the effect of that particular stimulus which is repeated. The initial equivalence of the two stimuli clearly indicates a convergence in the sense that they activate identical motoneurones. Therefore it seems justified to conclude that the habituation cannot be explained by decreased excitability of the motoneurones; the blocking must occur at an earlier stage of the spinal reflex arc where selective action upon a particular afferent input may occur (cf. Kastein, 1937). Prosser and Hunter (1936) arrived at a similar conclusion when studying the mechanism behind extinction of spinal reflexes in the rat.

The specificity of habituation in regard to the location of the stimulus deserves a few comments. The specificity implies that the habituation primarily affects the response to that particular stimulus which has been repeated. Non-repeated stimuli with a different locality may also lose in effectiveness by the habituation procedure, especially if this is continued long after the response to the repeated stimulus has been extinguished. This tendency to generalization is not seen in fig. 1, where the habituation to a certain stimulus was never allowed to continue far "below zero." In experiments of similar kind it was noted that the process of habituation could discriminate between abdominal stimuli that were 3–4 cm. apart and this distance was also found to represent the approximate limit of the subject's capacity to perceive the change of stimulus position.

Some experiments seemed to indicate that the habituation is specific also in regard to the quality of the abdominal stimulus. When a response to a weak electrical stimulus was totally extinguished by habituation a light tap within the same skin area would still evoke the response; and during habituation to this new stimulus, the electrical shock would sometimes regain its effect.

The abdominal skin stimulus not only evokes a contraction of the abdominal muscles but also a reciprocal inhibition of the trunk erector muscles (Kugelberg and Hagbarth, 1958). As shown in fig. 2 both the excitatory and the inhibitory effect of the stimulus is abolished by the habituation. This finding is in agreement with the conclusion that the

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habituation primarily affects the sensory rather than the motor division of the spinal reflex centre.

The habituation of the abdominal skin reflex may be regarded as a purposive reaction in the sense that the organism suppresses a spinal withdrawal response to a light skin stimulus which has proved to be not painful or deleterious. The habituation regularly occurred more quickly at low than at high intensities of stimulation and, with very strong taps or electrical stimuli, the response was frequently not extinguished, although it sometimes was reduced in size. The most striking effect of such noxious abdominal stimuli was that they frequently caused a sensitization to abdominal stimuli with a lower intensity.

Increase of excitability by nociceptive stimuli (*sensitization*).—In the experiment illustrated in fig. 3 the abdominal stimuli were applied in the epigastric region and the recording electrodes were inserted in the obliquus muscle. The stimuli were throughout the experiment delivered at a frequency of 5–20/min. The initial test stimulus was a weak tap in the skin which did not evoke any appreciable contraction. The next 3 stimuli were very much stronger and are best described as hard blows in the same epigastric region. Besides deforming the skin and the abdominal wall each of them caused a painful visceral sensation and brought about a vigorous contraction of the abdominal muscles. When, now, the weak test stimulus was reintroduced it was found to evoke a contraction, but as repetition went on the reflex gradually subsided until after 19 repetitions the skin stimulus again was ineffective. A new and longer series of epigastric blows (*B*) re-established the skin reflex which this time persisted after more than 130 repetitions. Even on the day after this experiment the test stimulus evoked a reflex which only with difficulty could be extinguished by habituation.

The painful visceral sensation was regularly accompanied by a vigorous abdominal contraction and there seems to be little doubt that the visceral stimulus in itself really evokes a reflex contraction of the abdominal muscles which is usually stronger than the reflexes elicitable from the skin. Earlier workers have described the tonic action of viscero-abdominal reflexes in man (Rauber, 1919; Bruns, 1920; Raagaard, 1941) and animal experiments have shown that stimulation of the splanchnic nerve causes a phasic contraction of the abdominal muscles (Downman, 1955).

In an abdominal blow, stimulation of the skin is automatically combined with the potent visceral stimulus and thus the experiment described (fig. 3) may be said to fulfil the requirements of a true conditioning procedure. This does not necessarily mean, however, that the pairing of the two stimuli plays any significant role in this particular experiment; the establishment of the skin reflex might be due to pseudo-conditioning (Grether, 1938, cf. also Hilgard and Marquis, 1940, pp. 41–43), which in this case would imply that the painful visceral stimulus by itself causes a

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non-specific sensitization of the spinal reflex centre. In order to elucidate this problem the following question may be raised: does the process of sensitization discriminate between abdominal stimuli of different locality in the sense that it maximally affects the response to that particular stimulus which in the course of sensitization precedes the visceral reflex? Sometimes epigastric blows caused a marked sensitization to epigastric skin stimuli but only a slight sensitization to abdominal skin stimuli at a different location. This kind of discrimination, however, could not always be demonstrated. Epigastric blows often caused a marked sensitization also to skin stimuli in the lower parts of the abdominal wall, and a typical feature of sensitization was a general increase of the receptive field so that abdominal skin reflexes could be elicited from more widespread areas of the trunk than normally. Usually a single hard blow was sufficient to cause sensitization but, as shown in fig 3, the effect had a tendency to persist longer if the blows were repeated several times. In classical conditioning experiments discrimination usually improves with increasing number of reinforcements but in the present experiments it was for obvious reasons necessary to restrict the number of hard blows and it was therefore difficult to evaluate the discriminatory capacity of the sensitization process.

Hard abdominal blows were found to be the most efficient sensitizing stimuli but a similar effect could be obtained also by painful abdominal skin stimuli. A series of painful electrical shocks on the abdominal skin surface often caused a long-lasting augmentation of abdominal reflexes to light taps. In this case it seems as if the pain stimuli by themselves cause a sensitization and thus the procedure resembles pseudo-conditioning. But another possibility also deserves consideration: probably a great variety of skin end-organs are excited by the electrical stimulus and it is conceivable that, due to various conduction velocities in the peripheral sensory fibres, a message from pressure and touch receptors will reach the spinal cord before the pain signals arrive and elicit the reflex. According to this argument the electrical stimuli may by themselves automatically bring about a conditioning or reinforcement of pressure or touch stimuli.

All stimuli which have been found capable of evoking sensitization are of such a character that they may be said to bring about an automatic pairing of conditioned and unconditioned sensory messages. Sensitization could be evoked only by those painful stimuli which by themselves elicited abdominal reflex contractions: painful stimuli applied to a skin area outside the receptive field of the reflex had no sensitizing effect. It is still unknown if a "pure" pain message from the abdominal skin surface or from the abdominal viscera can cause a sensitization to weak abdominal skin stimuli. In this connexion it is of interest to note that tabetic gastric crises may bring about an augmentation of abdominal skin reflexes (Bumke and Foerster, 1936). Such a sensitization would indicate that

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pseudo-conditioning occurs but it would not exclude the possibility that under normal circumstances automatic pairing of conditioned and unconditioned messages plays a significant role in the sensitization procedure. No matter how sensitization arises, it implies a capacity to make appropriate readjustments in the sense that the organism produces or revives a spinal withdrawal response to a light skin stimulus which by itself is not painful but which may be immediately followed by a painful stimulus. Evidently a short latency is an essential requirement for an appropriate withdrawal reaction and if the reflex is evoked already by the touch stimulus the latency will be shorter than if the reflex does not appear until the pain impulses arrives.

As indicated above, sensitization widens the receptive field of the abdominal skin reflex. After a series of epigastric blows, abdominal reflexes could sometimes be evoked by moderate skin stimuli at the level of the mammillary plane. The sensitization also increases the spatial irradiation of the reflex in the musculature of the abdominal wall. The reflex contraction evoked by a hard abdominal blow is not always restricted to the abdominal musculature; it often irradiates to the flexor muscles of the extremities and causes a general crouching of the body. A sensitized response to a moderate abdominal skin stimulus usually irradiates to a lesser extent even though it may involve some flexor muscles in the lower extremity. It is of some interest to conceive how with increasing strength of sensitization the abdominal skin reflex gradually emerges into a more widespread reaction which has a striking resemblance not only to startle responses (cf. Duensing, 1952) but also to the pathological abdominal mass reflexes sometimes encountered in spinal man (Head and Riddoch, 1920; Monrad-Krohn, 1954). This finding lends support to the assumption that the differences between these various reflexes are quantitative rather than qualitative (cf. Langworthy, 1930).

The processes of sensitization and habituation mutually counteract each other in the sense that one increases and the other decreases neural excitability within the spinal reflex centre. By training procedures where sensitization to one stimulus runs parallel with habituation to another it was possible to remodulate the function of the reflex centre in such a way that afterwards there was an increase in the response to the sensitized stimulus while the response to the habituated stimulus was unaffected or even decreased (fig. 4). It may be said that the discriminatory capacity of sensitization has been improved by the concurrent process of habituation and in this respect the result is comparable to "differential inhibition" in classical conditioning experiments.

Cerebral control of excitability.—The processes of habituation and sensitization are not exposed to direct voluntary control. Verbal instructions to suppress or to augment the reflex had no consistent effect. In other ways it was possible to demonstrate, however, to what a large extent

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habituation and sensitization depend upon cerebral functions. As will be shown, the strength of the abdominal skin reflex is correlated with the subject's state of apprehension in regard to painful abdominal stimuli. No doubt, the training procedures by themselves are liable to influence the subject's expectancy of abdominal pain: the apprehension is apt to decrease during the habituation procedure and increase during the course of sensitization. Fig. 5 summarizes the results of some experiments where more systematic attempts were made to modify the apprehensive or attentative state of the subject.

It is an old observation that abdominal skin reflexes are usually weak or absent if the stimuli are applied by the subject himself (Jendrassik, 1894; Munch-Petersen, 1902). In fig. 5 is shown the negative result of such a self-stimulation (A1) and the reflex that appears when an apparently identical stimulus is applied by the experimentator (A2 upper record). When this reflex had been extinguished by habituation (A3 above) the subject was told that next stimulus should be made harder. This false information caused a prompt restoration of the response to the succeeding light skin stimulus (A3 below). In another subject the test stimulus was so weak that initially it hardly evoked any reflex (B1 above) but after informing the subject that next stimulus should be hard and painful a reflex appeared on the test stimulus (B1 below). In this case sensitization has evidently been evoked by verbal suggestion. Also in next trial the test stimulus was initially insufficient to evoke a reflex (B2 above). The subject was assured that he was going to get one single hard blow and that the succeeding stimulus should again be weak. He got the hard blow and the succeeding test stimulus was as inefficient as the initial one (B2 below). Apparently no sensitization occurred when the subject was convinced that no further painful stimuli should be applied. In fig. B5 is shown an attempt to distract the subject's attention away from the abdominal events. After having noticed that the test stimulus was strong enough to evoke an abdominal reflex (above) a painful electrical skin stimulus was applied to the subjects left arm and while this stimulation was still going on and apparently attracted the subject's attention, no reflex could be evoked by the test stimulus (below).

Discussion

As shown in our previous study (Kugelberg and Hagbarth, 1958) the latency of the abdominal skin reflex may vary a great deal according to the central excitatory state and the intensity of the stimulus. It is only under optimal conditions that the latency is short enough to exclude a cerebral reflex arc. Longer latencies, however, may well be attributed to lengthening of spinal delay. A fact of relevance for the present discussion is that all responses, even those with the shortest latencies, are susceptible to habituation and sensitization.

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The fact that the reflex is spinal does not give any clue to the question of the central origin of the habituation and sensitization processes. Is the spinal cord in itself capable of initiating such plastic changes reminiscent of "learning"? This problem has attracted the interest of several workers but the results are controversial. There seems to be no definite evidence that conditioned reflexes can be established in an isolated spinal cord (Shurrager and Culler, 1940; Deese and Kellogg, 1949) but there is evidence that plastic changes like habituation may occur in the isolated spinal cord of lower mammals (Prosser and Hunter, 1936). In this connexion, the experiments on post-tetanic potentiation in the spinal cord are of particular interest (Eccles, 1953). It was recently shown by Granit, Pascoe and Steg (1957) that post-tetanic potentiation in an inhibitory spinal feed-back loop may cause a cumulative and relatively enduring depression of spinal neurone excitability. As a tentative assumption it may be proposed that habituation might be due to similar cumulative events in inhibitory feed-back loops within the central nervous system.

As shown by the experiments, illustrated in fig. 5, cerebral functions are engaged in the habituation and sensitization processes. It appears that these plastic phenomena are correlated or subordinated to mental processes like attention, expectancy or apprehension. Plasticity is a characteristic feature of neural function in higher centres, and it seems probable that most of the plastic changes, encountered in the present experiments, are of cerebral origin. In so far as the abdominal skin reflex can be said to "learn," this learning is probably a reflection of plastic changes occurring in the brain. Such a conclusion is in keeping with the fact that the process of habituation takes account, not only of preceding sensory stimuli, but also of the total sensory situation in which these stimuli occur.

According to this reasoning the present results should be explained on the basis of a tonic cerebral outflow which in a selective fashion adjusts the performance of the spinal reflex centre. As shown above, the process of habituation does not primarily affect the motoneurones but rather the interneurones within this reflex centre. Sometimes a sensory input is allowed to reach the final common pathway, sometimes not; and this checking mechanism appears to be capable of discriminating between sensory stimuli of slightly different location and/or quality. Evidently, a sensory block, evoked by habituation, may be cancelled by the sensitization process, which strives to increase the excitability within the spinal reflex centre. The events imply that the spinal internuncial relays are susceptible to an intricate cerebral control, capable not only of initiating but also of maintaining enduring functional changes within the spinal internuncial pool. By such a control the analytical capacity of the brain may be constantly reflected in spinal behaviour patterns, allowing for appropriate reactions with a minimal latency.

On clinical evidence it has earlier been proposed that spinal inter-

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neurones are susceptible to cerebral governors (cf. Duensing and Schneider, 1940) and animal experiments give ample support to the opinion that such susceptibility exists. The fact that electrical stimulation of various cerebral structures may affect the activity of spinal interneurones has been deduced from experiments on slow cord potentials (Lindblom and Ottosson, 1956), sensory tract potentials (Hagbarth and Kerr, 1954), reflex responses (Kleyntjens, Koizumi and Brooks, 1955) or single unit discharges within the grey matter or the sensory tracts of the spinal cord (Lloyd, 1941; Hagbarth and Fex, 1958). Artificial stimulation of brain structures, however, gives little information about the physiological significance of the regulating mechanism involved. An interesting approach to this problem was presented by Hernández-Peón (1955) who showed that, in unrestrained animals, the evoked potentials in specific sensory pathways are susceptible to habituation, and that the amplitude of these responses is correlated to the attentive state of the animal. Their investigations include a variety of primary sensory pathways, all of which are found susceptible to centrifugal control (for ref. *see* Hernández-Peón, 1957). According to Galambos *et al.* (1956) post-synaptic auditory responses in the cochlear nucleus may not only be depressed by habituation, but also augmented by conditioning procedures (cf. also Hernández-Peón, Scherrer and Jouvet, 1956).

The spinal sensory inflow is partly distributed to motor nuclei in the same or adjacent segments, partly to ascending sensory tracts. The present results do not give any definite clue as to whether the ascending influx may be affected by habituation and sensitization processes, but some concurrent observations seem to indicate such a possibility. During the habituation procedure the subject sometimes perceives an illusion of declining stimulus intensity and during sensitization he sometimes gets an illusion of increasing intensity of the test stimulus. In a similar way, during the stress of a painful experience there is not only a suppression of the reflex response to a moderate abdominal test stimulus (fig. 5, B3) but also a definite impairment of the subject's ability to perceive this test stimulus.

It is quite possible that the processes of habituation and sensitization not only affect the interneurones but also the motoneurones of the spinal reflex centre. The effect of sensitization especially may partly be due to increased excitability of the abdominal motoneurones, either evoked directly or indirectly through the efferent gamma-loop (Granit, 1955). The process of sensitization, however, is not exposed to direct voluntary control; voluntary excitation of the motoneurones does not yield the effect of a sensitization procedure.

The present results seem to have some bearing upon conditioning experiments in general. According to Pavlov's original hypothesis a conditioned reaction arises by the establishment of new functional connexions at the cortical level between the "centre" of the conditioned stimulus and

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the "centre" of the unconditioned stimulus (Pavlov, 1928). Later work has indicated that the brain-stem reticular formation may also play an important role in the establishment of conditioned reflexes (Yoshii, Pruvot and Gastaut, 1957; Jouvet and Hernández-Peón, 1957). That certain structures of the brain are indispensable for the establishment of conditioned reflexes does not necessarily imply, however, that the functional connexions arise within these structures. The network of interneurones in spinal or other subcortical reflex centres might be regarded as the substrate of an innumerable number of potential functional connexions. Within these centres functional paths can be closed or opened and this adjustment may be accomplished by a centrifugal outflow emerging from those levels of the nervous system where the total sensory situation can be properly analysed and where intricate plastic changes may occur.

Micro-electrode studies of spinal interneurone activity (recordings from grey matter or sensory tracts) have shown that a single unit not only may be activated or inhibited from a great variety of peripheral sensory sources (Kolmodin and Skoglund, 1954; Frank and Fuortes, 1955; Eccles, Fatt and Landgren, 1956; Laporte, Lundberg and Oscarsson, 1956; Kolmodin, 1957) it may also be exposed to excitatory or inhibitory influences from the brain (Hagbarth and Fex, 1958). If in a spinal, decerebrate or anæsthetized preparation a single interneurone is found to react in a non-specific way to a great number of varied peripheral sensory stimuli, this merely signifies that a great number of converging functional connexions do exist. It must not be presupposed that all these potential functional connexions are simultaneously open to transmission in the intact organism. The establishment of specific temporary connexions (conditioning) may be regarded as an assorting process, which selectively rejects or adopts among an innumerable number of potential functional connexions. Recent micro-electrode studies in the cortex indicate that during the process of conditioning there is primarily an elimination of widespread generalized responses rather than a simple establishment of new connexions (Ricci, Doane and Jasper, 1957). If it is assumed that a conditioned response emerges out of an original subthreshold tendency to react in that manner to the conditioned stimulus, then it may be difficult to maintain a clear distinction between sensitization and conditioning processes (cf. Martino and Alibrandi, 1938).

It might be questioned whether the processes of habituation and sensitization are mainly "laboratory products" or whether they ordinarily play any significant role for the organism. Probably our erect posture involves a certain susceptibility to abdominal blows and it appears that the main function of the abdominal reflexes is to protect visceral organs which are not shielded by the skeleton. It must be of benefit for the organism that this reflex defence is plastic, that it can "learn" from earlier experience and that it constantly takes account of the total sensory situation. It is

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probably not a coincidence that the abdominal skin reflex usually is most vivid in the upper part of the abdominal wall: in the area overlying the pain-sensitive cœliac plexus sensitization is most likely to occur. And why is it that the abdominal skin reflex usually is weak in subjects with a thick layer of abdominal fat? Possibly, the fat may act as a damper so that sensitizing painful visceral stimuli are less likely to occur.

It has been demonstrated that mental processes, like attention, expectancy and apprehension of a painful stimulus, play an important role in the regulation of the abdominal skin reflex. It is therefore reasonable to suspect that cerebral disturbances, involving impairment of these mental processes, may affect the abdominal reflex performance. It remains to be determined whether or not sensitization may occur in e.g. lobotomized patients who do not perceive the normal discomfort of painful stimuli.

It would be of interest to know which cerebrospinal paths are engaged in the plastic regulation of the spinal reflex centre. Since this regulation is relatively independent of direct voluntary control it may be concluded that the paths engaged are not identical with those subserving voluntary motor performance. This certainly does not exclude the possibility that elements within the pyramidal system take part in the plastic regulation. The loss of the abdominal skin reflex as a result of pyramidal lesions indicates a spinal release from tonic excitatory influences and the augmentation of the reflex, sometimes encountered in extrapyramidal disorders, suggests a release from tonic inhibition (cf. Monrad-Krohn, 1954; Duensing, 1952). It may well be that the abdominal skin reflex could be of greater diagnostic value if account was taken not only of the size of the reflex but also of its plastic behaviour, its susceptibility to habituation and sensitization and its ability to react in an appropriate way to verbal suggestion.

Summary

The human abdominal skin reflex constitutes an example of a spinal withdrawal reaction which can easily be analysed in the intact and unrestrained organism. The present electromyographic study of the normal behaviour of this reflex has led to the following conclusions.

(1) Repeated application of a non-painful abdominal skin stimulus leads to habituation which is specific to the location and quality of the given stimulus. The decrement of the reflex during habituation is due to a blockage of internuncial transmission rather than a lowering of motoneurone excitability.

(2) The habituation implies a capacity of the organism to suppress a spinal withdrawal reaction to a light skin stimulus which by repetition has proven to be not painful or deleterious.

(3) The effect of habituation may be counteracted by a process of sensitization which is brought about by painful abdominal stimuli (visceral

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or cutaneous). Such deleterious stimuli may evoke enduring augmentation of abdominal skin reflexes to light touch stimuli.

(4) Sensitizing stimuli have the following characteristics: (*a*) they do by themselves evoke strong reflex contractions tending to cause a general crouching of the body; (*b*) they are of such a nature that they may be said to bring about automatic pairing of touch and (visceral or cutaneous) pain messages. It cannot be excluded that the effect of sensitization partly depends upon such automatic pairing of conditioned and unconditioned stimuli.

(5) Sensitization lowers the stimulus threshold, widens the receptive field and extends the irradiation of the reflex. It implies a capacity of the organism to produce or revive a spinal withdrawal response to a light skin stimulus which by itself is not painful but which may be associated with a painful stimulus.

(6) By training procedures where sensitization to one abdominal stimulus runs in parallel with habituation to another it is possible to remodulate the function of the reflex centre in such a way that afterwards there is an increase of the response to the sensitized stimulus while the response to the habituated stimulus is unaffected or even decreased. It is postulated that some well-known features of the human abdominal skin reflex may be explained on the basis of such previous training.

(7) As judged from experiments on autostimulation, verbal suggestion or distracting pain stimulation, the habituation and sensitization processes not only take account of the total sensory situation, they are also intimately correlated to mental processes like attention, expectancy or apprehension.

(8) Even though the reflex is mediated by a spinal reflex arc it has the ability to "learn" in a similar way as a conditioned cerebral reaction. This "learning" is interpreted as a reflection of cerebral events; it is postulated that a cerebral outflow directs spinal internuncial transmission in such a way that temporary spinal connexions can be established, thus allowing for appropriate responses with minimal latency.

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PLATE XLIV

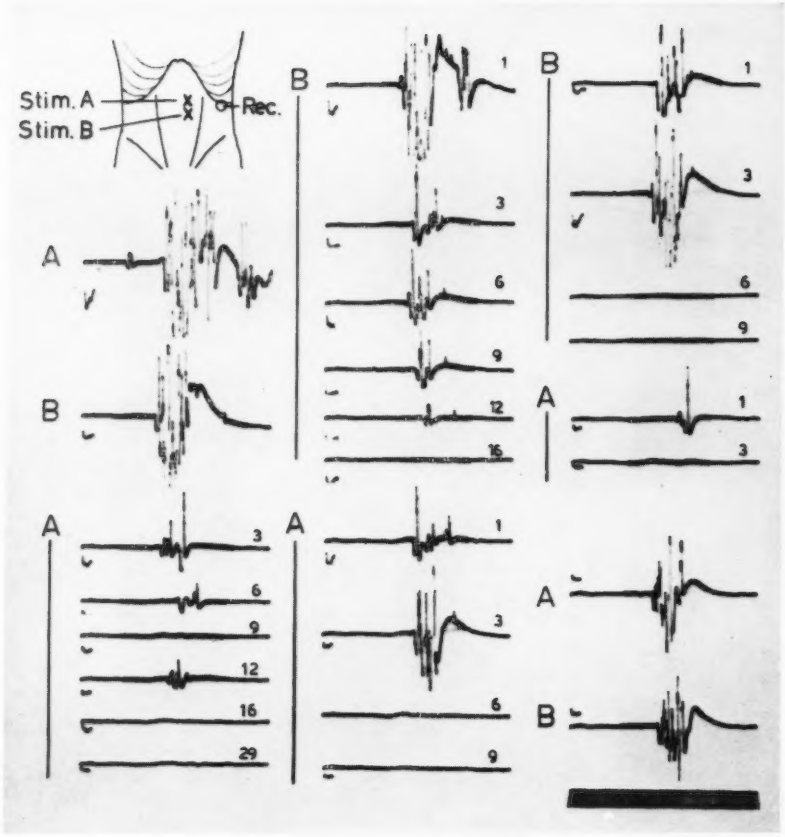

FIG. 1.—Specificity of habituation in regard to the location of the stimulus. *Stim. A* and *B* are identical electrical stimuli applied 4–5 cm. apart on the abdominal skin surface. Recording electrodes are inserted in the upper part of the external obliquus muscle. During the entire course of the experiment the stimuli (alternatively *A* or *B*) are applied in succession with a stimulus interval of 5–10 sec. The fig. should be read in vertical rows from left to right. Vertical lines on the left indicate which stimulus is being repeated and the numbers on the traces indicate how many times a stimulus has been applied in unbroken succession. The two last records (lower right) were obtained 15 min. after the end of the experiment and show the persisting effect of habituation. For further description *see* text. Time 500/sec.

To illustrate article by K. E. Hagbarth and E. Kugelberg.

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PLATE XLV

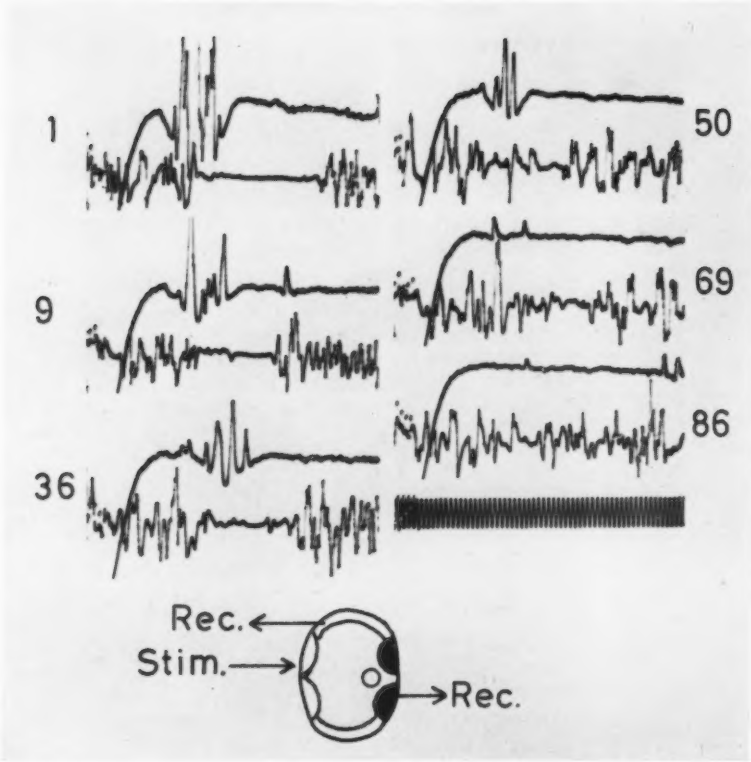

FIG. 2.—The excitatory as well as the inhibitory effect of the stimulus is diminished by habituation. Simultaneous recording (about the level of Th.9) from the right external obliquus muscle (upper record) and the left erector trunci muscle (lower record). The subject was sitting, the abdominal muscles being relaxed and the erector muscles voluntarily activated. Repeated electrical skin stimuli are applied in the epigastric region (stimulus interval 5–10 sec.). The numbers indicate how many times the stimulus had been repeated when the record was taken. Time 500/sec.

To illustrate article by K. E. Hagbarth and E. Kugelberg.

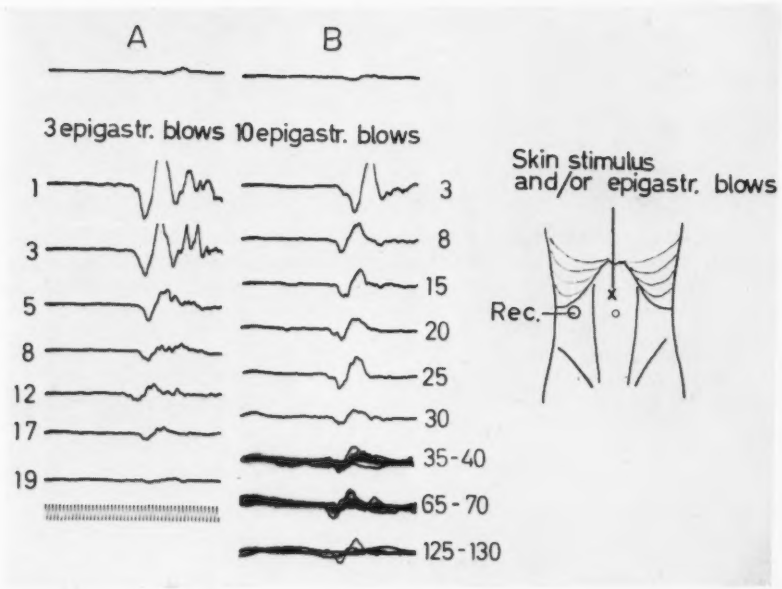

FIG. 3.—Sensitization of an abdominal skin reflex. Recording from the right external obliquus muscle. Repeated mechanical stimuli (moderate skin taps sometimes replaced by hard blows) are applied in the epigastric region (stimulus interval 5–10 sec.). In A an initial tap is followed by 3 epigastric blows and then the taps are readopted. In B 10 epigastric blows are inserted. Experiments A and B were performed in succession without interrupting the sequence of stimulation. For further description *see* text. Time 500/sec.

To illustrate article by K. E. Hagbarth and E. Kugelberg.

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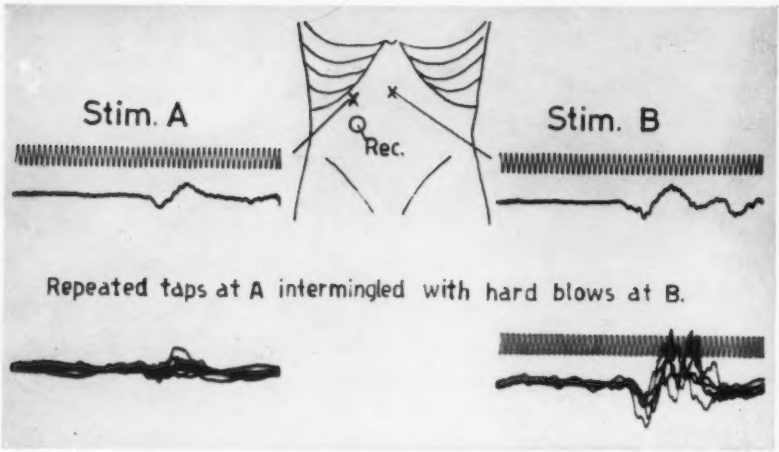

FIG. 4.—Habituation to one skin stimulus running parallel with sensitization to another. Moderate skin taps are applied alternatively in the right (*stim. A*) and in the middle (*stim. B*) epigastric region. Recording electrodes are inserted in the external obliquus muscle. Initially *stim. A* and *B* are equivalent in the sense that they evoke abdominal reflexes of similar magnitude (upper record). During the training procedure moderate taps in the right epigastric region are intermingled with hard blows in the middle epigastric region. Afterwards the response to *stim. B* is exaggerated and the response to *stim. A* is unaffected (or decreased). Time 500/sec.

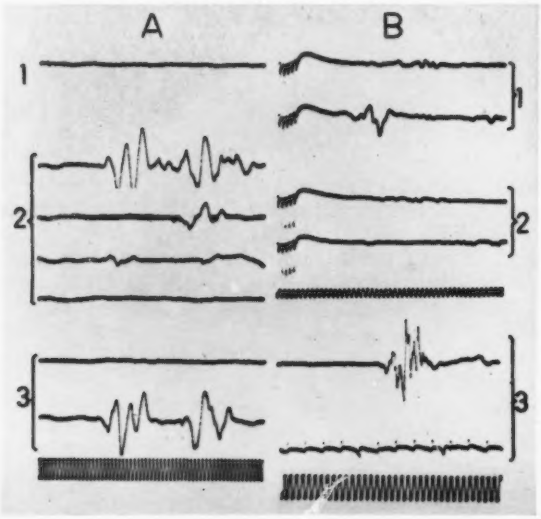

FIG. 5.—Experiments on autostimulation, verbal suggestion and distracting pain stimuli. *See* full description in the text. A and B3: skin taps in the epigastric region. Recording from the upper part of the left external obliquus muscle. B1 and 2: Electrical skin stimuli in the epigastric region. Recording as in A. Time 500/sec.

To illustrate article by K. E. Hagbarth and E. Kugelberg.

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HIPPOCAMPAL PROJECTIONS AND RELATED NEURAL PATHWAYS TO THE MID-BRAIN IN THE CAT

BY

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RECENT studies in the rat (Guillery, 1956; Nauta, 1956) have confirmed much earlier descriptions of widespread distributions of the fornix system to the diencephalon and the rostral mid-brain regions. Besides the well-known massive hippocampal projections to the septal region (Ganser, 1882) and the mammillary body (Gudden, 1881), fornix components have been traced from the hippocampus to the preoptic region and the hypothalamus (Cajal, 1911), to the anterior nuclear complex and rostral intralaminar nuclei of the thalamus (Gudden, 1881; Vogt, 1898; Cajal, 1911), and to the rostral part of the central grey mid-brain substance (Edinger and Wallenberg, 1902).

The wide sphere of influence outlined by such distributions of the fornix system is undoubtedly further expanded by secondary neural pathways arising from the recipient structures of the direct hippocampal projection. Of such secondary pathways, those arising in the septal area (Nauta, 1956) and lateral hypothalamic region (Guillery, 1957) have recently been analysed in some detail in the rat by experimental methods. It is apparent from these studies that, in the rat, both structures project directly to the mid-brain by way of the medial fore-brain bundle, while an additional pathway of septal origin follows the stria medullaris to the medial nucleus of the habenular complex. The mesencephalic projections from both regions could be traced to an extensive medial region of the mid-brain, including Tsai's (1925) ventral tegmental area, those from the septum also to the voluminous raphe nucleus of Bechterew (n. centralis tegmenti superior) in the caudal half of the mid-brain. From the mammillary body, the mammillo-tegmental tract had already been traced experimentally (v. Valkenburg, 1912; Sanz Ibáñez, 1935) to Gudden's deep tegmental nucleus, a medial cell group closely associated with Bechterew's raphe nucleus. These findings appeared to indicate the existence of a convergence area for secondary hippocampal projections in a fairly

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circumscript medial zone of the mid-brain tegmentum. The present experiments were designed to subject the generality of this notion to further experimental test by tracing the mesencephalic projections arising in several further structures known to receive direct or indirect hippocampal pathways.

Needless to say, it is unlikely that fibre systems traced in this manner represent discharge channels of hippocampal impulses exclusively. It is known, for example, that the septal and preoptic regions receive projections not only from the hippocampus, but also from the amygdaloid complex (Gloor, 1955; Nauta and Valenstein, 1958). The medial fore-brain bundle, which serves as the main connexion of these regions with the mid-brain, must consequently be regarded as a common trajectory for descending projections of various origin. Most, if not all, such projections have their most cranial representation in palæocortical and subcortical structures in the basal and medial walls of the cerebral hemisphere, collectively designated by the term "limbic system" (for the historical derivation of this term *see* MacLean, 1952, 1954). The fibre systems to be discussed in the present study are thus extremely heterogeneous, anatomically as well as, no doubt, functionally. They are composed of direct projections from "limbic" structures, as well as the trans-synaptic subcortical extensions of such pathways. Where collective reference seems necessary, they will be referred to as "limbic pathways," in an attempt to obviate the use of the undoubtedly too restrictive terminology "rhinencephalic" or even "olfactory." However, this is done with the understanding that the term, in its present usage, is hardly less vague than designations such as "extrapyramidal."

A complication in the course of the present experiments was presented by the observation of some significant differences between mammalian species in regard to some of the primary and secondary hippocampal projections studied. Several of the previous findings in the rat proved not to be immediately applicable to the cat. Comparative data to be published elsewhere (Valenstein and Nauta, in preparation) suggest that such inter-specific differences consist of variations in the number of synaptic interruptions rather than the ultimate distribution of the pathways involved. Where relevant, such variations will be mentioned in the description of the findings.

Material and Methods

The present report is based upon findings in approximately 20 cats in which small electrolytic lesions had been placed by the aid of a stereotactic instrument. The survival times varied between eight and fourteen days. Axon degeneration was demonstrated histologically in frozen sections by the Nauta and Gygax (1954) silver technique, and recorded in projection drawings of selected sections.

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OBSERVATIONS

(1) *Hippocampal projections.*—The direct hippocampal projections contained in the fornix system were found to be similar in many respects to those described in the rat by Guillery (1956) and Nauta (1956). As in the rat, fibres of hippocampal origin were traced via the massive precommissural fornix to the septal nuclei and preoptic region, and through the fornix column to certain rostral thalamic cell groups, to the lateral hypothalamic region, and to the mammillary body. However, direct hippocampal projections to the medial hypothalamic region, conspicuous in rodents (Cajal, 1911; Nauta, 1956) could not be identified with certainty in the cat. A further difference from the findings in the rat was noted in the number of fornix fibres distributing to the rostral region of the central grey mid-brain substance: whereas only few such fibres could be demonstrated in the rat, this fornix component appears to be quite massive in the cat. It is formed by numerous fibres which bypass the mammillary body and curve steeply dorsalward a short distance behind this structure in bundles which course along the mid-line, cross in part, and distribute to the ventral half of the central grey substance at the level of Darkschewitsch' nucleus and the rostral half of the oculomotor complex.

(2) *Projections from the septal nuclei.*—As in the rat, it proved to be difficult to obtain an accurate picture of the subcortical projections from the septal region, as lesions of the region invariably involve hippocampal projection pathways. However, it appears certain that, in the cat also, the medial part of the stria medullaris contains a fairly massive septal projection to the medial nucleus of the habenula. As in the rat, this pathway, long considered to be of hippocampal origin, was found degenerated only following certain lesions in the septal region; it was not affected in any case of hippocampal lesion. In the cat, this septo-habenular tract appears to originate largely in the caudal region of the supracommissural septum.

The precommissural fornix is joined in its septal trajectory by numerous fibres of septal origin. The resultant fibre group, which forms a large part of Zuckerkandl's "olfactory bundle of Ammon's horn" is one of the most massive roots of the medial fore-brain bundle. Whereas its hippocampal constituents appear not to distribute beyond the lateral preoptic region, septal fibres, in the cat as well as in the rat (Nauta, 1956), continue farther caudalward in the medial fore-brain bundle and distribute to the entire extent of the lateral hypothalamic region. In the rat, a considerable number of such septal fibres even extend into the mesencephalon, where they terminate in the ventral tegmental area (i.e. the region immediately ventral to the medial half of the red nucleus), and in Bechterew's superior central tegmental nucleus in the caudal half of the mid-brain. In the cat, however, such direct mesencephalic projections from the septal region appear to be much less well developed

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in both volume and extent. In the present experiments, only a few degenerated fibres could be traced from septal lesions via the medial fore-brain bundle to the ventral tegmental area; none were followed to Bechterew's nucleus. It is apparent from these findings that the septal projection in the cat does not extend much farther caudalward than do the direct hippocampal pathways.

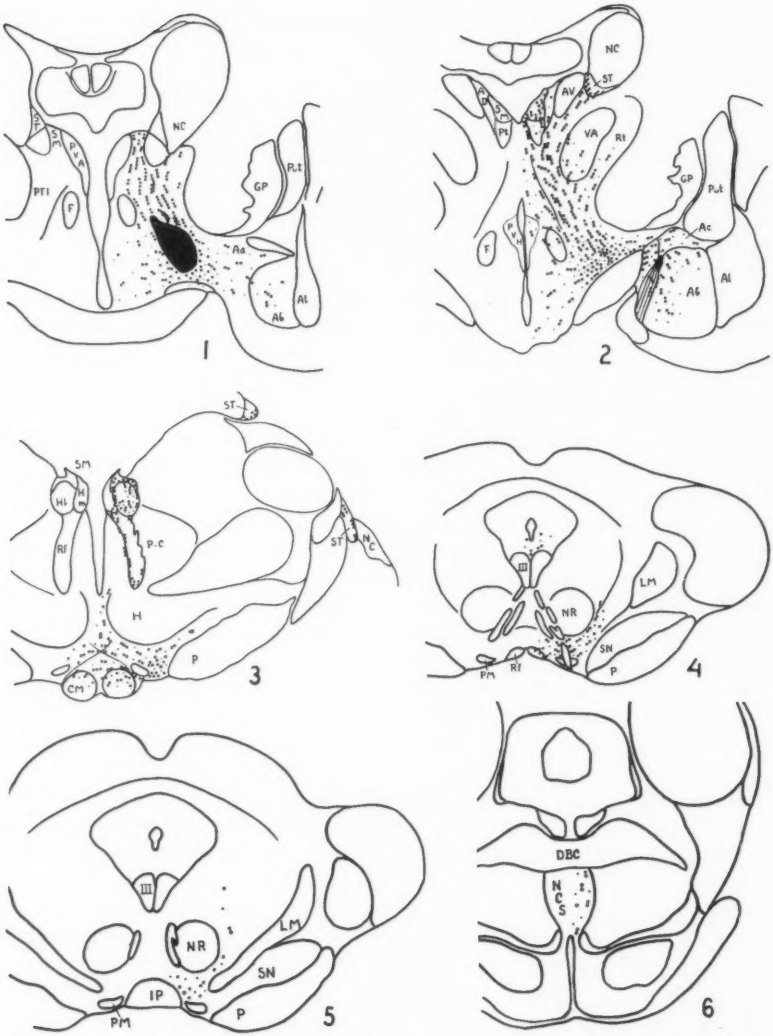
(3) *Projections from the lateral preoptic and hypothalamic regions.*—It is evident from the foregoing observations that the lateral preoptic region is an important distribution area of hippocampal and septal projections, while many fibres of septal origin and a limited number of hippocampal fornix fibres in addition distribute to the lateral hypothalamic region. It therefore appeared of interest to determine the projections arising in this general region. It must be realized that the lateral preoptic and hypothalamic regions compose a continuous longitudinal cell group interstitial to the medial fore-brain bundle. The individual distributions of preoptic and hypothalamic efferents contained in the medial fore-brain bundle can therefore be identified only by careful comparison between the results of lesions located at various frontal levels. Such efferents can best be described by the aid of two cases.

A. *Lesion of the lateral preoptic region: Case CT* 124.—In this case, the lesion had been produced by a slender electrode introduced at an angle of about 45 degrees from the contralateral side and at the same time oriented slightly caudalward. It was localized in the lateral preoptic region coextensive with the rostral half of the optic chiasma. The caudal pole of the lesion is indicated in fig. 1. The fornix column was in no way involved in the defect. Only the fibre degeneration extending caudalward from the lesion will be described.

As shown by figs. 1–6, three main tracts of degenerating fibres can be followed from the lesion. The most voluminous of these is incorporated in the medial fore-brain bundle, while a second massive pathway follows the inferior thalamic peduncle, and a third group of degenerating fibres spreads laterally to the amygdaloid complex.

(*a*) The degeneration in the medial fore-brain bundle extends caudalward through the lateral zone of the hypothalamus and, beyond it, into the mid-brain. Profuse terminal degeneration accompanies the system throughout the lateral hypothalamic nucleus. A considerable number of degenerating axons, however, spreads medially from the bundle in a rather diffuse fashion and can be followed to the anterior and dorsomedial nuclei, some also to the ventromedial nucleus of the hypothalamus. Some of these medial offsets also distribute to the supraoptic nucleus (fig. 1), and a slightly larger number can be traced to the paraventricular hypothalamic nucleus (fig. 2).

Farther caudally it is evident that the mammillary body receives a considerable number of fibres from the medial fore-brain bundle (fig. 3).



FIGS. 1–6.—Fibre degeneration following a lesion of the lateral preoptic region (Case CT 124). The caudal part of the lesion is indicated in jet black in fig. 1. Coarse stipple indicates degenerating fibres of passage; fine stipple terminal degeneration. Abbreviations *see* p. 339.

Degenerating axons enter the structure from the lateral side and distribute rather diffusely in both medial and lateral cell groups. Some such fibres cross transversely into the contralateral medial mammillary nucleus,

Other degenerating fibres of the same group distribute to the supramammillary region and to the extreme rostral part of the central grey mid-brain substance. It is of interest to note here that medial fore-brain bundle afferents to the mammillary body were already observed by Tello (1936) in young mouse embryos. According to Tello's findings, the medial fore-brain bundle precedes the fornix system in embryonic development as the major source of afferent supply to the mammillary body.

Sections caudal to the mammillary body show degenerating components of the medial fore-brain bundle in the ventral tegmental region of Tsai, adjoining the ventral aspect of the red nucleus (fig. 4). A moderate number of longer fibres of this group can be followed past the interpeduncular nucleus to the caudally adjacent raphe nucleus of Bechterew (n. centralis tegmenti superior, fig. 6) in which they terminate.

(*b*) A second massive system of degenerating fibres extends from the lesion in the dorsomedial direction, following the inferior thalamic peduncle. In the thalamus, this system traces a wide path, with offsets to the nuclei reticularis, ventralis anterior, parataenialis, and anterodorsalis (fig. 2), as well as to the n. dorsomedialis. Numerous further degenerating fibres enter the stria medullaris (figs. 1, 2), while a smaller number extend laterally in the ventral fibre capsule of the anterior nuclear complex and join the stria terminalis (fig. 2). Those enclosed in the stria medullaris run caudalward to an area of profuse terminal degeneration which occupies most of the lateral habenular nucleus (fig. 3). Some fibres of the same group bypass the habenula and join the fasciculus retroflexus with which they reach the ventral surface of the brain-stem, where they appear to leave the bundle, entering the ventral tegmental area, and mingling with the medial fore-brain bundle components terminating in the same region (fig. 4).

The degenerating fibres which join the stria terminalis follow the bundle in its semicircular course to the amygdaloid complex. The ultimate distribution of these elements cannot be determined accurately, as they blend with

(*c*) a third, rather diffuse group of degenerating axons which extends laterally from the preoptic lesion through the substantia innominata, and enters the amygdaloid complex from the medial side (figs. 1–2). These fibres, part of which travel caudally over some distance alongside the optic tract, distribute to the anterior, medial, central, and basal amygdaloid nuclei; none appear to reach the lateral nucleus of the complex (fig. 2).

B. *Lesion of the caudal part of the lateral hypothalamic region: Case CT* 99.—By contralateral approach, using an angle of approximately 45 degrees, a small electrolytic lesion was placed, immediately dorsal and slightly lateral to the mammillary body (fig. 7). The lesion and the electrode track had interrupted part of the supramammillary decussation, the common stem ("pars principalis," Koelliker) of the mammillothalamic and

mammillotegmental tracts, as well as a major part of the medial fore-brain bundle. A small part of the posterior hypothalamic nucleus was pierced by the electrode track. It is of importance to note that Forel's field H, the cerebral peduncle, and the subthalamic nucleus were in no way involved in the lesion.

Immediately caudal to the lesion, the medial fore-brain bundle appears as the central structure in a widespread field of fibre degeneration. It occupies its characteristic position ventral to the red nucleus (fig. 8). Spreading from the bundle in a laterodorsal direction are degenerating slender fascicles which distribute to the tegmental region adjoining the substantia nigra on the dorsal side. This lateral spread of the medial fore-brain bundle appears to be similar to, although more massive than that observed following lesions in the preoptic region. More caudally, however, a significant difference from the results of preoptic lesion is noted in the form of numerous degenerating axons which curve around the lateral side of the red nucleus (fig. 9) and collect in scattered fasciculi running caudalward immediately dorsal to the stratum lemnisci. Throughout its course along the ventral border of the mid-brain tegmentum, this group of degenerating fasciculi releases numerous fibres which sweep dorsalward through the tegmentum (fig. 9). Some such fibres appear merely to traverse the tegmentum *en route* to the central grey mid-brain substance; others, however, terminate diffusely in the central tegmental region. Farther caudally, slightly rostral to the frontal level of the trochlear nucleus, this entire lateral fibre system initiates a rather abrupt dorsal sweep through the tegmentum (fig. 10). On this dorsocaudal trajectory also, it is accompanied throughout by signs of diffuse tegmental termination, while additional fibres to the central grey mid-brain substance can be followed dorsally. Finally, at the level of the trochlear nucleus, the remaining fibres of the system collectively enter the central grey mid-brain substance (fig. 11), where they are lost among numerous further degenerated fibres distributing in the region.

The remaining part of the medial fore-brain bundle continues caudalward through the ventral tegmental area, immediately dorsal to the fasciculus retroflexus and the mammillary peduncle (figs. 8, 9). This medial group of degenerating fibres is more massive but otherwise comparable with that observed following preoptic lesion. As in the preceding case, it can be traced along the lateral aspect of the interpeduncular nucleus (fig. 9) and from here dorsalward along the median plane of the caudal mid-brain tegmentum. Its main termination appears to be in Bechterew's raphe nucleus (figs. 12, 25) and a narrow adjoining medial tegmental region. Unlike the preoptic projection, a number of fibres of the group continue beyond the raphe nucleus and enter the central grey substance near the mid-line (figs. 12, 13).

A further degenerated fibre system descending to the mid-brain consists

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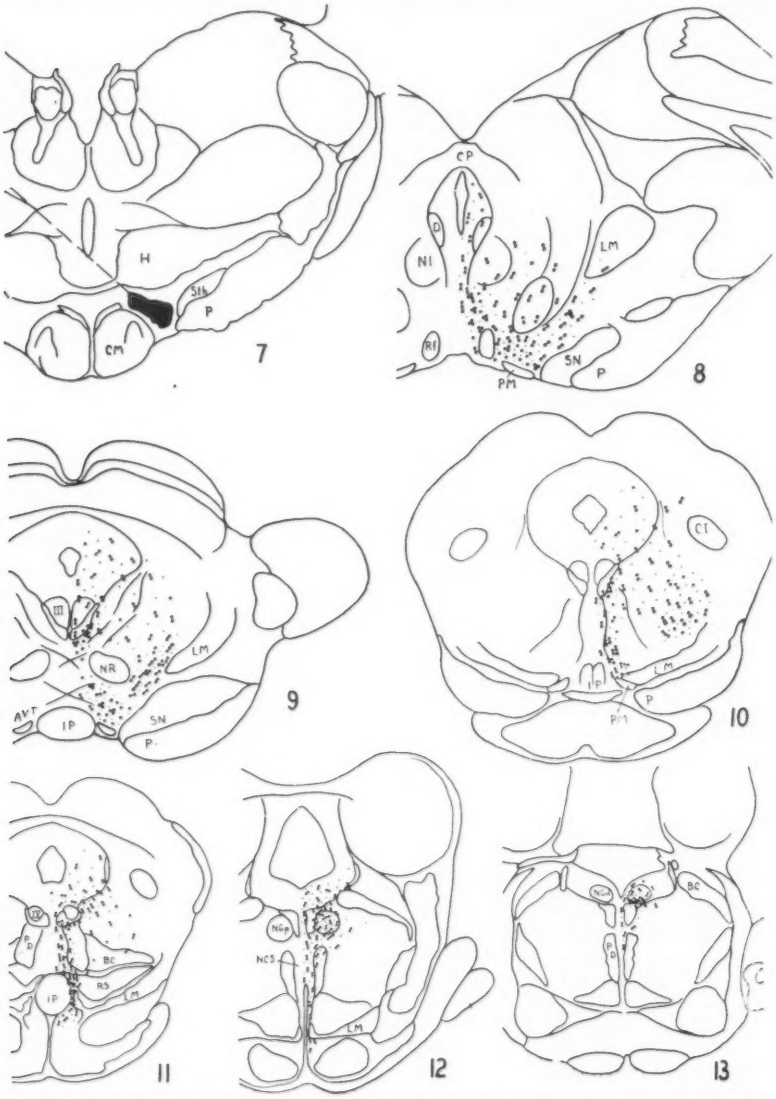
of slender fascicles which extend from the lesion, first in the dorsomedial direction (fig. 8), then caudalward immediately ventral to the medial



FIGS. 7–13.—Fibre degeneration observed following a small lesion in the caudal part of the lateral hypothalamus (Case CT 99). The lesion is indicated in jet black in fig. 7. Coarse dots: degenerating fibres of passage; fine stipple: terminal degeneration.

longitudinal fasciculus (figs. 9–11). Throughout its descending course the system is easily identifiable by its relative compactness. It appears to mingle to some extent with the ventral fibres of the medial longitudinal fasciculus. There can be little doubt that this degenerating fibre group represents the mammillo-tegmental tract: its appearance in the present case corresponds closely to Sanz Ibáñez (1935) observations in Marchi material. A large proportion of its fibres can be followed to a degenerating plexus of extremely fine axon ramifications in the deep ("ventral") tegmental nucleus of Gudden (figs. 12, 26), but many other fibres of the bundle enter the central grey substance and terminate in the medial part of Gudden's dorsal tegmental nucleus and its surroundings (fig. 13). Dense terminal degeneration in Gudden's tegmental nuclei as observed in the present case was consistently found lacking following hypothalamic lesions which had spared the mammillary body and the pars principalis of Vicq d'Azyr's bundle.

Finally, the slight involvement of the posterior hypothalamic nucleus noted above has caused the disintegration of a fairly considerable number of fibres descending in Schütz's dorsal longitudinal fasciculus. It is impossible to trace these fibres caudalward, due to their mingling with large numbers of degenerating fibres of different origin which enter the central grey substance at various frontal levels. However, as no fibre degeneration can be identified in the central grey substance one millimetre caudal to Gudden's dorsal tegmental nucleus, it seems doubtful that Schütz's fibre system contains elements descending directly from the hypothalamus beyond the isthmus region.

(4) *Projections from the habenula: Case VA* 4.—The foregoing cases have confirmed the existence of two major projections to the habenular complex. One such pathway originates in the supracommissural part of the septal region, joins the stria medullaris as a branch of the fornix bundle, and terminates in the medial habenular nucleus. The second (Koelliker, 1896) appears to arise from the lateral preoptic region as a component of the inferior thalamic peduncle; it also joins the stria, but its habenular termination is confined to the lateral habenular nucleus. Both pathways could be interpreted to represent indirect projections from the limbic system, in turn relayed to the mesencephalon via the habenulo-interpeduncular tract (fasciculus retroflexus of Meynert). Two cases of degeneration in the fasciculus retroflexus will be described next.

(*a*) In *Case VA* 4 a small lesion had been placed immediately ventral to the habenular complex, by contralateral and rostrocaudal approach (fig. 14). It had completely severed the fasciculus retroflexus just below its exit from the habenula. Also involved was a small part of the periventricular grey substance ventral to the habenular complex. The posterior commissure was entirely intact.

The fasciculus retroflexus is completely degenerated and can easily

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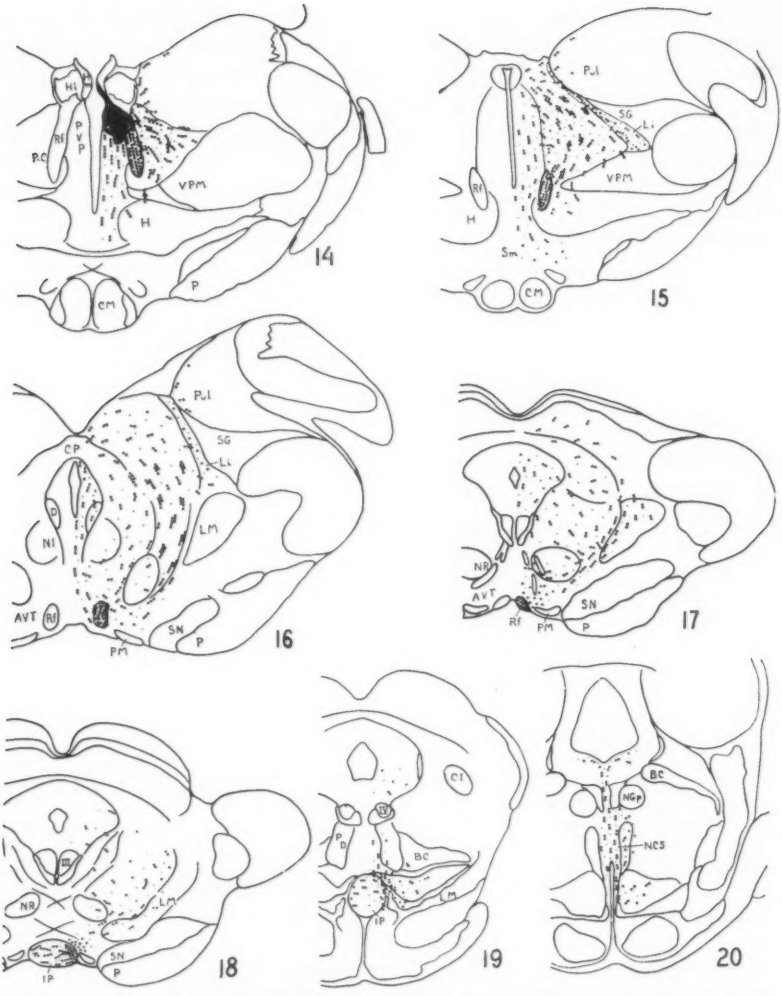

FIGS. 14–20.—Fibre degeneration resulting from complete interruption of the fasciculus retroflexus (Case VA 4). Coarse dots: degenerating fibres of passage; fine stipple: terminal degeneration. Abbreviations *see* p. 339.

be followed in its characteristic course to the basal surface of the mesencephalon and thence caudalward. This case, however, demonstrates a greater complexity of the caudal habenular projections than would be recognized from a cursory examination of the fasciculus retroflexus in normal material: apart from the compact bundle of Meynert, a more

diffuse system of arcuate fascicles, here degenerated, sweeps in broad curves lateralward from the lesion through the parafascicular nucleus—centre median complex (figs. 14, 15), then caudoventrally through the lateral tegmentum of the upper mesencephalon (fig. 16), and finally medialward underneath the red nucleus (figs. 17, 18). From here caudalward this more diffuse pathway of apparently habenular origin follows the compact fasciculus retroflexus on the lateral and dorsal sides. It is of great interest to note that this diffuse habenular pathway, throughout its arcuate trajectory, releases numerous fibres which distribute to the parafascicular nucleus—centre median complex and the adjacent nucleus limitans (figs. 14, 15), as well as to an extensive central and lateral tegmental region of the upper mid-brain (figs. 15–17). Some such fibres spread into the central grey substance where they are lost among fairly numerous degenerating axons interrupted by the periventricular lesion ventral to the habenula.

The termination of the compact fasciculus retroflexus in the interpeduncular nucleus is evident at levels represented by figs. 18 and 24. Slender fascicles of extremely fine degenerating fibres course medialward from the bundle, traverse the entire width of the interpeduncular nucleus, and turn back abruptly in a characteristic "figure 8" fashion as described by Cajal (1911). Degenerating terminal fibres are difficult to identify in this system of extremely fine axons; those that can be interpreted as such are more numerous on the side ipsilateral to the lesion.

Few if any fibres of the compact fasciculus retroflexus appear to continue caudalward beyond the interpeduncular nucleus. The more diffuse concomitant fibre group, however, by-passes the interpeduncular nucleus on the lateral side (figs. 18, 19) and, near the caudal pole of the nucleus, gradually curves dorsalward, spreading over Bechterew's nucleus centralis tegmenti superior and an adjacent narrow tegmental region outlined by the predorsal fasciculus (figs. 19, 20). The longest fibres of the group (fig. 20) extend dorsalward along the mid-line and enter the caudal part of the central grey substance, where their distribution appears to be restricted to a cell group described as "fountain nucleus" by Sheehan (1933).

(*b*) *Case CT* 112.—Among several additional cases of involvement of Meynert's bundle this case is of particular interest, as the lesion was entirely restricted to the medial habenular nucleus. In this instance, the compact fasciculus retroflexus showed massive degeneration, but the more diffuse concomitant lateral fibre system was entirely normal. This case suggests that the origin of the latter projection is confined to the lateral habenular nucleus.

Discussion

The present study has served to emphasize the existence of various pathways by which the hippocampus, as well as other members of the limbic system, can transmit its influence to the mid-brain. In the cat as

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in the rat (*see* Nauta, 1956), only one such pathway seems to represent a direct hippocampal projection. It consists of a number of fornix fibres which by-pass the mammillary body and distribute to the rostral part of the central grey mid-brain substance. It is interesting that this direct hippocampo-mesencephalic projection is much more strongly developed in the cat than it is in the rat.

Far more massive than this direct projection are the indirect limbic connexions with the mid-brain. Such connexions, established by pathways arising in the septal region, lateral preoptic and hypothalamic regions, mammillary body, and habenula, follow the medial fore-brain bundle and the mammillo-tegmental tract as well as the route outlined by the stria medullaris and fasciculus retroflexus. The pathways in question are illustrated diagrammatically by fig. 21 A and B. As indicated by the present findings, direct hippocampal projections articulate with such secondary limbic pathways mainly in the septal and lateral preoptic regions and in the mammillary body, to a lesser extent also in the lateral hypothalamus. The amygdaloid complex, as indicated by Gloor's (1955) electrophysiological findings as well as by anatomical data (Nauta and Valenstein, 1958) projects to the septal and lateral preoptic regions and could there connect with the same secondary pathways[1].

It is of importance to note that the septal and lateral preoptic regions constitute a nodal area in the limbic projection channels. In this extensive region, primary hippocampal and amygdaloid projections appear to overlap at least to a certain extent, and from it, two separate pathways to the mid-brain originate: a ventral fibre system incorporated in the medial fore-brain bundle (fig. 21 A) and a more dorsal pathway which forms the stria medullaris, synapses in the habenula, and is continued by the fasciculus retroflexus (fig. 21 B). Of these two secondary fibre systems, the medial fore-brain bundle is the most difficult of analysis, for it contains long axons as well as numerous synaptic chains of shorter connexions. Of the many fibres of this bundle which enter the mid-brain, some have their origin in the lateral preoptic region (in the rat such fibres even originate in the septum), but a far larger number arise more caudally, i.e. in the lateral hypothalamus.

In spite of considerable diversity of origin and trajectory, all of the major limbic pathways to the mid-brain share certain characteristics in their caudal distribution. Somewhat schematically, all three: the medial fore-brain bundle, mammillo-tegmental tract, and fasciculus retroflexus, can be said to have a dual distribution in the mid-brain. Of each, a lateral component terminates in central and lateral tegmental

[1]Actually, the anatomical data have demonstrated that the distribution of the direct amygdalo-septal projection is restricted to the basal part of the septal region. It appears justifiable, however, to assume that secondary pathways exist which allow for a further spread of the amygdaloid projection to more dorsal septal areas.

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regions (broken lines in fig. 21 A and B), while the remaining fibres distribute over a smaller or larger part of an extensive medial and paramedian mid-brain region to be discussed below. None of the pathways in question appears to extend beyond the level of the isthmus.

(1) *Lateral mesencephalic projections of the limbic system.*—The more lateral projections of the limbic system distribute widely in central and lateral tegmental regions, as follows:

(*a*) A prominent pathway of lateral distribution is established by a lateral component of the medial fore-brain bundle (broken lines in fig. 21 A).

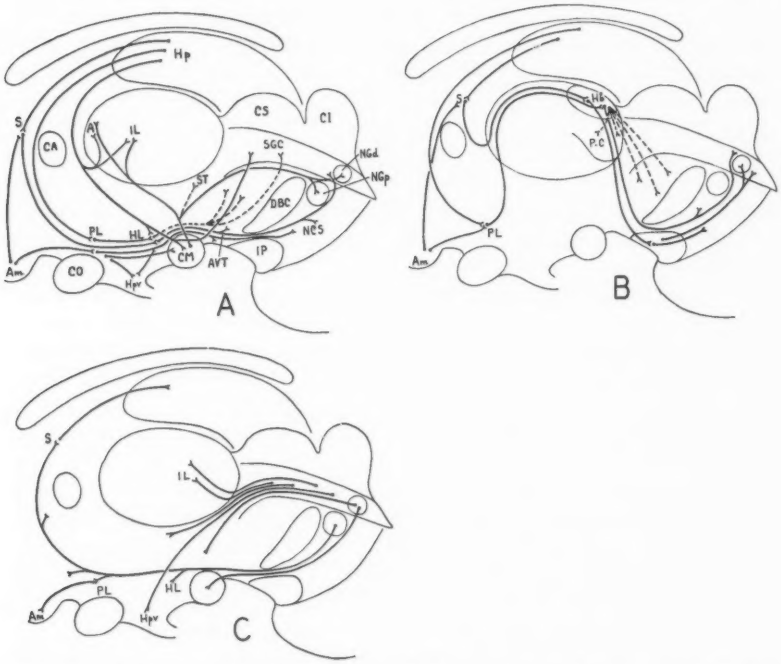

FIG. 21.—Diagrammatic representation of the connexions between some limbic fore-brain structures and the mid-brain, as described in the text. Broken lines indicate projections to central and lateral regions of the brain-stem tegmentum. Pathways distributing to medial tegmental regions ("limbic mid-brain area") are indicated by solid lines. A: limbic pathways incorporated in the fornix, medial fore-brain bundle, and mammillo-tegmental tract. B: limbic pathways following the stria medullaris and fasciculus retroflexus. C: ascending mesencephalic projections related to the limbic system. Abbreviations: A, anterior nuclear complex of thalamus; Am, amygdaloid complex; CA, anterior commissure; CO, optic chiasma; HL, lateral hypothalamic region; Hp, hippocampus; Hpv, medial and periventricular hypothalamic regions; IL, intralaminar thalamic nuclei; S, septal region; SGC, central grey substance, ST, subthalamic region. Other abbreviations *see* p. 339.

Significantly, it degenerates following lesions in the lateral hypothalamus, but lesions in the lateral preoptic region do not appreciably affect it. In its present description (*see* Case CT 99) it appears to correspond at least to some extent to a lateral part of the "basal olfactory tract" described by Wallenberg (1901) in the rabbit, and to a component of Bischoff's (1900) "fasciculus olfacto-mesencephalicus" of the hedgehog. It possibly also corresponds in part to the dorsal and posterior hypothalamo-tegmental tracts described by Crosby and Woodburne (1951) in the monkey.

This more lateral projection in all likelihood represents one of the main pathways by which the lateral hypothalamus transmits its influence, via synapses in the mid-brain reticular formation, to the visceral motor nuclei farther caudally in the neuraxis. Its wide spread in the mid-brain tegmentum could supply an explanation for the diffuseness of the transtegmental hypothalamic discharge demonstrated in physiological experiments (Magoun, Ranson and Hetherington, 1938; Ranson and Magoun, 1939). In addition, however, it must be realized that this lateral hypothalamic projection spreads over the tegmental region occupied by the diffuse and multineuronal reticulo-thalamic and reticulo-subthalamic pathways which are believed to form the anatomical substratum of Moruzzi and Magoun's (1949) diffuse cortical activating system (*see* Nauta and Kuypers, 1958). By connecting synaptically with the shorter, mesencephalic components of this widespread ascending brain-stem system, the hypothalamus, and by its mediation the limbic structures, could conceivably influence basic patterns of cortical activity related to states of wakefulness or sleep. The present anatomical findings would thus suggest a possible interpretation of the drowsy or sleep-like states accompanying inflammatory or traumatic lesions in or immediately behind the caudal hypothalamus (v. Economo, 1918; Ranson, 1939; Ranson and Magoun, 1939; Nauta, 1946; Collins, 1954, and others) as a result of interference with a phasic descending excitatory discharge from the hypothalamus, via lateral components of the medial fore-brain bundle articulating with ascending projections from the mid-brain reticular formation.

(*b*) A second pathway of somewhat comparable distribution to the central and lateral tegmental region appears to originate in the lateral nucleus of the habenula (broken lines in fig. 21 B). It consists of numerous arcuate fibres which spread over the parafascicular nucleus, centre median and nucleus limitans as well as farther caudalward over a broad area of the rostral mid-brain tegmentum (*see* the present Case VA 4). This projection does not extend as far caudally in the central and lateral mid-brain tegmentum as does the lateral hypothalamic projection described above.

(*c*) An additional lateral projection related to the limbic system is represented by a fairly substantial lateral offset from the mammillotegmental tract, distributing to Forel's field H and the zona incerta. It

terminates among the complex conduction systems ascending and descending through the subthalamic region.

(*d*) Further potentially important connexions of the limbic system with the central and lateral tegmental regions are established by a massive and diffuse fibre system which originates in the central grey mid-brain substance and spreads radially over most of the tegmental cross section, as well as over the deep layers of the superior colliculus (Weisschedel's (1937) radiatio grisea tegmenti, *see below*). In considering the possible functional significance of this massive radial pathway, however, it must be borne in mind that the central grey substance receives afferents from many sources outside the limbic system (*see below*).

It is appropriate at this point to recall the somatic motor phenomena which have been elicited by stimulation of the amygdala and hippocampus (Kaada *et al.*, 1953, 1954; Magnus and Lammers, 1956; Votaw, 1957). It seems possible that such motor phenomena, like the visceral effects of stimulation of limbic fore-brain structures, are mediated by some or all of the above-mentioned limbic pathways to the subthalamus and central tegmental regions of the mid-brain reticular formation.

In the Australian marsupial, the phalanger, Adey *et al.* (1956) described a projection from the entorhinal area which follows the stria medullaris and, without synapsing in the habenula, distributes directly to dorsolateral regions of the mid-brain tegmentum. In the cat, a comparable pathway could not be identified in the present experiments. Two cases in which the stria medullaris was interrupted rostral to the habenula failed to show evidence of fibre degeneration in the lateral mid-brain tegmentum. However, this discrepancy may be due to interspecific variation which, as pointed out before, is quite commonly encountered in comparative studies of the limbic projection systems.

(2) *Limbic pathways distributing in medial mid-brain regions.*—Numerous fibres of the medial fore-brain bundle, mammillo-tegmental tract, and fasciculus retroflexus distribute to a medial tegmental region which has its rostral beginning in Tsai's ventral tegmental area, extends caudalward along the base of the mesencephalon where it includes the interpeduncular nucleus, and then arches dorsalward along the caudal aspect of the brachial decussation as the nucleus centralis tegmenti superior of Bechterew, which in turn becomes continuous with the central grey substance caudal to the trochlear nucleus (*see* fig. 21 A). The dorsal and deep tegmental nuclei of Gudden and the ventral part of the central grey substance must be included in the same mid-brain region.

The region in question largely lies outside the massive stream of the reticulo-thalamic and reticulo-subthalamic conduction systems, from which, however, it receives short connexions (Nauta and Kuypers, 1958). Since, excepting the central grey (*see below*), it appears to be related specifically to the limbic system, it seems justifiable to use the term

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"limbic mid-brain area" as a schematic designation of the region here discussed.

(*a*) In the region thus outlined, the medial fore-brain bundle distributes to the ventral tegmental area, Bechterew's tegmental nucleus and the caudal part of the central grey substance. The corresponding fibres originate in the lateral preoptic region (in the rat also in the septum (Nauta, 1956)), and especially in the lateral hypothalamus. In the cat, the contributions from the preoptic region appear not to extend farther caudalward than the rostral part of Bechterew's nucleus (Case CT 124). The present findings agree to some extent with Wallenberg's (1901) observation of medial fore-brain bundle termination in ventral and medial tegmental regions in the rabbit, with Tello's (1936) tracing of similar fibres to the regions of Gudden's nuclei in the mouse, and with Guillery's (1957) report of medial fore-brain bundle distribution to the ventromedial tegmentum and the caudal end of the central grey substance in the rat. In their typical position ventral to the red nucleus, the medially distributing components of the medial fore-brain bundle described above also correspond to the anterior hypothalamo-tegmental fibre system observed in the monkey by Crosby and Woodburne (1951) who, however, could not follow the system beyond the level of the oculomotor nerve exit in that species.

Although this medial component of the medial fore-brain bundle is quite massive, physiological findings (Magoun, Ranson and Hetherington, 1938) indicate that it does not represent the main pathway by which the hypothalamus exercises its influence upon the visceral motor system. Instead, such findings tend to emphasize the importance for such functions of more laterally placed transtegmental pathways, probably represented by the lateral component of the medial fore-brain bundle discussed above.

(*b*) The fasciculus retroflexus appears to have a dual mode of distribution in the limbic mid-brain area (fig. 21 B). Its most conspicuous, compact part terminates in the interpeduncular nucleus, where it articulates with Ganser's (1882) "tegmental bundle of the interpeduncular nucleus" (*see* Koelliker's (1896) figs. 635 and 643), a massive system of relatively fine fibres which extend from the nucleus caudodorsally along the median plane and distribute to Bechterew's nucleus and the caudal end of the central grey, probably including Gudden's dorsal tegmental nucleus. Additional fibres of the fasciculus retroflexus, however, form a massive and more diffuse lateral group which by-passes the interpeduncular nucleus and distributes directly to Bechterew's nucleus and the caudal part of the central grey substance. This fibre group undoubtedly corresponds to the "habenulo-tegmental tract" described by Bürgi and Bucher (1955) in the cat.

(*c*) Finally, the mammillo-tegmental tract was traced to both the

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dorsal and deep tegmental nuclei of Gudden. In contrast to Guillery's (1957) findings in the rat, the termination of this fibre system in the deep tegmental nucleus, although characterized by an extreme fineness of the terminal axon arborizations, is quite profuse in the cat. The mammillo-tegmental tract was originally traced to this nucleus by Gudden (1889), and later by Koelliker (1896), v. Valkenburg (1912), Sanz Ibáñez (1935), and others. It has not been possible in the present material to trace any fibres of the mammillo-tegmental tract caudalward into the pontine and medullary tegmentum as described by Tello (1936) and Sanz Ibáñez (1935).

Dorsal longitudinal fasciculus and central grey substance.—It would seem appropriate to include the dorsal longitudinal fasciculus of Schütz among the medial pathways related to the limbic system. For a discussion of the earlier findings in regard to this fibre system reference is made to Ingram's (1940) excellent review of hypothalamic anatomy. Although the prevailing direction of conduction appears to be ascending (Bucher and Bürgi, 1945; Johnson, 1953), the bundle contains descending fibres which appear to have a wide origin in medial and periventricular hypothalamic cell groups, distribute to the ventral half of the central grey substance, and are probably augmented by axons arising in the central grey proper. Undoubtedly, the dorsal tegmental nucleus of Gudden receives a number of such periventricular hypothalamic fibres, but the system rapidly dwindles caudal to this nucleus and no part of it seems to extend beyond the level of the abducens nucleus. It even appears doubtful from a study of normal material that Schütz's system is massively continued caudalward by fibres arising from the dorsal tegmental nucleus and its surroundings, as was suggested by Ariens-Kappers, Huber and Crosby (1936). Rather, experimental anatomical data suggest that Schütz's periventricular system and the dorsal longitudinal fasciculus essentially represent an association system of the medial hypothalamus and the central grey mid-brain substance.

As indicated by the present data, further limbic pathways distributing to the central grey are formed by: (*a*) hippocampal and possibly septal fibres to the rostral one-third of the structure; (*b*) fibres from the lateral hypothalamus via the lateral component of the medial fore-brain bundle to at least the rostral and middle thirds, and (*c*) a variety of further paths from the lateral hypothalamus, habenula, and interpeduncular nucleus to the caudal one-third. The central grey substance, however, also receives many afferents of non-limbic origin. Such afferents are, for example, contained in the "spinothalamic" tract and in the diffuse ascending reticular pathways (*see* Nauta and Kuypers, 1958), as well as in the brachium conjunctivum (Thomas *et al.*, 1956; Mehler, unpublished). It is important to note that, on the efferent side, the central grey connects with the hypothalamus (*see below*), and through a massive and diffuse system of radial

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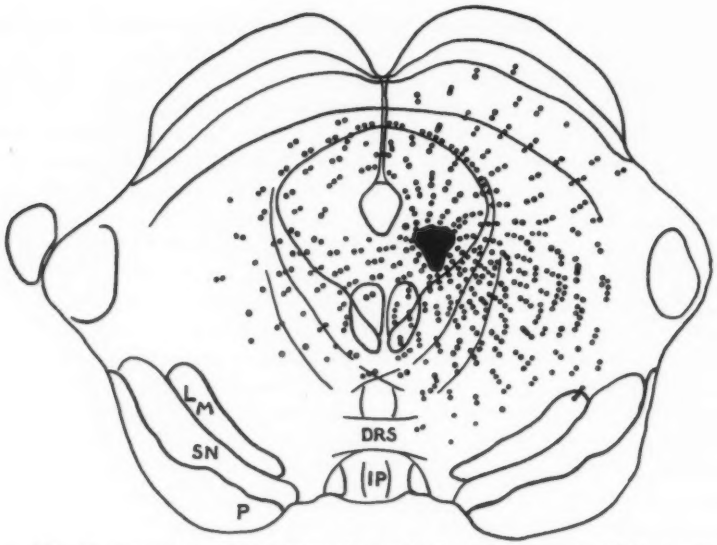

FIG. 22.—Degeneration of Weisschedel's "radiatio grisea tegmenti," in a case of sagittal-tubular lesion of the ventral half of the central grey substance (CT 116).

fibres (Weisschedel's (1937) "radiatio grisea tegmenti," *see* fig. 22) with almost the entire cross section of the mid-brain tegmentum and the superior colliculus. The latter fibre system appears to furnish a massive link between the limbic structures and the widespread ascending and descending tegmental conduction systems.

Ascending pathways related to the limbic system.—The close association of the medial mid-brain area with the limbic fore-brain structures is further emphasized by the distribution of ascending projections arising in the area. Such projections (*see* fig. 21 C) are represented by at least two fibre systems: (*a*) the ascending component of Schütz's dorsal longitudinal fasciculus which appears to originate throughout the length of the central grey substance inclusive of Gudden's dorsal tegmental nucleus, and (*b*) the system of the mammillary peduncle which arises from both the dorsal and ventral tegmental nuclei, possibly also from adjoining tegmental regions, and appears to receive further contributions from the ventral tegmental area (for a review of the pertinent literature *see* Ingram, 1940; Guillery, 1956; Nauta and Kuypers, 1958). The ascending component of Schütz's system ends in part in the intralaminar thalamic nuclei (Nauta and Kuypers, unpublished), but the majority distributes to periventricular and medial hypothalamic cell groups and to the dorsal hypothalamic area. The mammillary peduncle, on the other hand, connects massively with the mammillary body, but a large part of the bundle

continues rostralward in the medial fore-brain bundle, distributing to the lateral hypothalamic and preoptic regions and to the medial septal nucleus (Guillery, 1956; Nauta and Kuypers, 1958), augmented by further ascending projections from the lateral hypothalamus (Guillery, 1957). The medial septal nucleus, in turn, has been shown to project back to the hippocampus (Daitz and Powell, 1954), while the present findings indicate the existence of a similar recurrent projection from the preoptic region to the amygdaloid complex (*see* the present Case CT 124).

The limbic system—mid-brain circuit.—Comparing these ascending fibre systems with the limbic projection pathways, a striking reciprocity appears in the connexions between the limbic fore-brain structures and the "limbic mid-brain area." Substantial escape pathways from this circuitous neural apparatus would seem to lead mainly in three directions: to the medial hypothalamic region, to the diffuse ascending and descending conduction systems of the mid-brain tegmentum (*see* diagram in fig. 23), and to the anterior and intralaminar nuclei of the thalamus.

Of these escape routes, those to the medial hypothalamus merit special emphasis, as this region (Hpv in fig. 23) appears to be the part of the

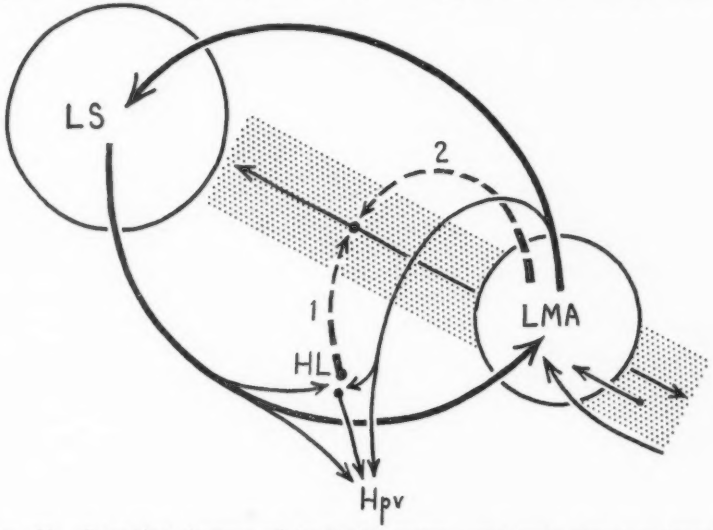

FIG. 23.—Simplified diagram of the limbic system—mid-brain circuit as described in the text. Broken arrows indicate collateral projections from the circuit to central and lateral regions of the mid-brain tegmentum (shaded): arrow 1 summarizes the lateral limbic pathways indicated by broken lines in fig. 21 A and B, arrow 2 represents Weisschedel's "radiatio grisea tegmenti" from the central grey substance. Abbreviations: LMA, "limbic mid-brain area"; LS, limbic fore-brain structures (hippocampus, septal region, amygdala); HL, lateral hypothalamic region; Hpv, medial and periventricular hypothalamic regions.

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hypothalamus most directly involved in neural mechanisms controlling anterior hypophysial functions. As indicated in greatly simplified form in fig. 23, the medial hypothalamic region receives offsets from both the descending and ascending limbs of the limbic system—mid-brain circuit. Such afferents reach the region directly (from the limbic fore-brain structures via the stria terminalis and medial fornix components, from the limbic mid-brain area via Schütz's bundle), as well as indirectly over the lateral hypothalamic and preoptic regions. The supraoptic nucleus of the hypothalamus is probably connected with the same circuit via the lateral preoptic regions from which it receives short fibres (*see* Case CT 124). In view of these collateral connexions, it appears reasonable to assume that the limbic system—mid-brain circuit can influence hypothalamic mechanisms controlling anterior and posterior hypophysial as well as visceromotor functions. The reciprocity in the connexions between the limbic fore-brain structures and the medial mid-brain area tends to suggest a mutual engagement of both brain regions in mechanisms subserving visceral and endocrine homeostasis.

Although somewhat separated spatially from the major diffuse conduction pathways of the brain-stem, the mesencephalic pole of the circuit, especially its central grey substance component, nevertheless receives afferents ascending from the anterolateral fasciculus of the spinal cord, as well as offsets from the "mainstream" of ascending reticular conduction (Nauta and Kuypers, 1958). Such afferent connexions (*see* fig. 23) would seem to furnish a likely route whereby the limbic system—mid-brain circuit could be activated by impulses of sensory origin. The limbic mid-brain area could thus represent a major relay in the afferent pathways involved in, for example, the anterior pituitary response to physical stress. It is, however, not possible at the present time to preclude the existence of further pathways connecting the diffuse ascending reticular conduction pathways with the hypothalamus. Such additional connexions could conceivably originate along the subthalamic and intralaminar trajectories of the ascending reticular pathways; their existence, however, remains to be demonstrated.

Finally, it appears likely that, besides lemniscal and extralemniscal sensory impulses, certain neocortical mechanisms can affect the neural mechanisms discussed in the present paper. In spite of much speculation, the anatomical substratum for such neocortico-limbic interaction is almost entirely obscure; it would seem to hold a lively challenge for future investigation.

Summary

Direct and potential (i.e. transsynaptic) hippocampal projection pathways to the mid-brain were traced experimentally in the cat by the aid of the Nauta-Gygax silver technique. Conclusions are as follows:

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(1) Direct hippocampo-mesencephalic projections appear to distribute only to the rostral part of the central grey substance.

(2) Indirect hippocampal pathways, in part interrupted by further relays, and probably also representing indirect projections of the amygdaloid complex, originate in the septum and in the lateral preoptic and hypothalamic regions, as well as in the mammillary body. Such pathways reach the mid-brain in three fibre systems, viz. the medial fore-brain bundle, the fasciculus retroflexus, and the mammillo-tegmental tract.

(3) Each of these three bundles has a dual distribution in the mid-brain: part of their fibres terminate in extensive central and lateral regions of the tegmentum, while the remaining component distributes to various subdivisions of a paramedian mid-brain region encompassing the ventral part of the central grey substance, Tsai's ventral tegmental region, interpeduncular nucleus, Bechterew's n. centralis tegmenti superior, and Gudden's dorsal and deep tegmental nuclei.

(4) The connexions with this medial ("limbic") mid-brain region are reciprocated by ascending pathways, part of which ultimately lead to the hippocampus and amygdaloid complex. Such ascending connexions appear to close a limbic system—mid-brain circuit, which in turn has extensive collateral connexions with the hypothalamus, as well as with the mesencephalic components of the diffuse ascending and descending reticular conduction systems.

Acknowledgments

The author is greatly indebted to Mrs. Mildred H. Albrecht, Miss Ruth Fernstrom, Mrs. Hertha Middleton, and Mr. Gordon Fletcher for their technical assistance in this study.

Abbreviations in Figures 1–20

Aa: anterior amygdaloid area; Ab: basal amygdaloid nucleus; Ac: central amygdaloid nucleus; AD: n. anterodorsalis thalami; Al: lateral amygdaloid nucleus; AV: n. anteroventralis thalami; AVT: ventral tegmental area of Tsai; BC: brachium conjunctivum; CI: capsula interna; CM: mammillary body; CP: posterior commissure; D: n. Darkschewitsch; DBC: decussation of brachium conjunctivum; DRS: decussation of rubrospinal tract; F: fornix; GP: globus pallidus; H: field H of Forel; Hl: n. lateralis habenulæ; Hm: n. medialis habenulæ; IP: n. interpeduncularis; Li: n. limitans thalami; LM: medial lemniscus; NC: n. caudatus; NCS: n. centralis tegmenti superior (Bechterew); NGd: n. tegmenti dorsalis (Gudden); NGp: n. tegmenti profundus (Gudden); NR: n. ruber; P: cerebral peduncle; P-C: parafascicular nucleus—centre median; PD: fasciculus predorsalis; PM: mammillary peduncle; Pt: n. paratenialis thalami; PTI: inferior thalamic peduncle; Pul: pulvinar thalami; Put: putamen; PVA: n. periventricularis anterior thalami; PVH: n. paraventricularis hypothalami; PVP: n. periventricularis posterior hypothalami; Rf: fasciculus retroflexus (Meynert); RS: rubrospinal tract; Rt: n. reticularis thalami; SG: n. suprageniculatus; Sm: supramammillary region; SM: stria medullaris; SN: substantia nigra; ST: stria terminalis; STh: n. subthalamicus; Va: n. ventralis anterior thalami; III: n. oculomotorius.

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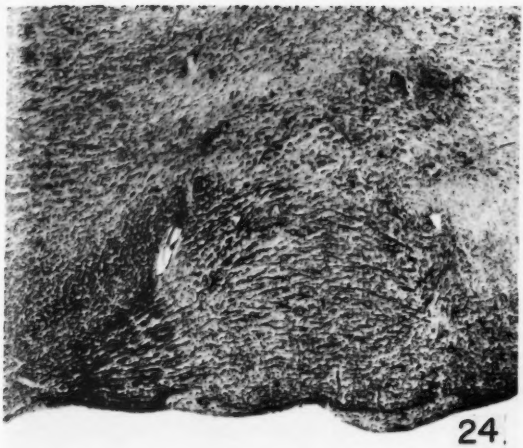

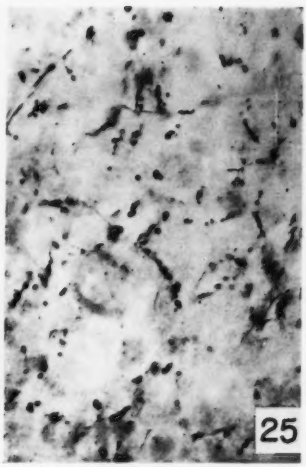

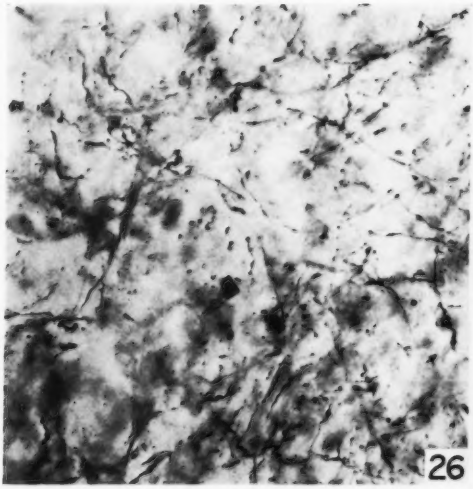

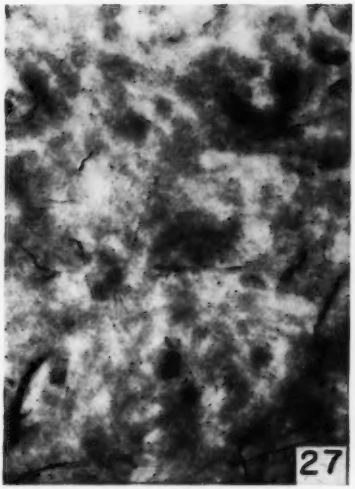

FIG. 24.—Unilateral degeneration of the fasciculus retroflexus following interruption of the bundle at its exit from the habenula (Case VA 4). Note the compact bundle releasing slender fascicles into n. interpeduncularis, and the more diffuse degenerating fibre group dorsal to it. ×45.

FIG. 25.—Axon degeneration in Bechterew's n. centralis tegmenti superior following caudolateral lesion of the hypothalamus (Case CT 99). ×600.

FIG. 26.—Degeneration of fine axons in Gudden's deep tegmental nucleus following ipsilateral lesion of the mammillo-tegmental tract (Case CT 99). ×600. Compare with fig. 27.

FIG. 27.—Absence of axon degeneration in Gudden's deep tegmental nucleus contralateral to lesion of mammillo-tegmental tract. Same case as fig. 26. ×600.

To illustrate article by Walle J. H. Nauta.

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EXPERIMENTAL PRODUCTION OF UNILATERAL NEGLECT IN MONKEYS

BY

KEASLEY WELCH AND PETER STUTEVILLE[1]

FOLLOWING the creation of a small specific lesión in the frontal lobe of the monkey, there occurs a change in behaviour which is characterized by irresponsiveness to stimuli of various kinds on the opposite side of the body and in the opposite half of space. The features of this disorder resemble very closely those of unilateral neglect as seen in man.

Portions of the experimentally produced syndrome have been described in the past, and although well known, have received little study. The visual and motor aspects of the disturbance have been well described, first by Bianchi (1895). He observed that after unilateral frontal lobectomy in the monkey, in addition to mental disturbance and impairment of head and trunk movements toward the opposite side, there was relative disuse of the extremities on that side and a visual change indistinguishable from an homonymous hemianopsia.

METHOD

Twenty-two animals were studied. The great majority of the experiments were carried out in African green monkeys (*Cercopithecus athiops sabæus*), a few in an unidentified species of macaque.

The surgical procedures were done under sterile precautions with standard technique. The lesions were made using a small sucker tip and subpial suction.

EXPERIMENTAL OBSERVATIONS

The lesion responsible for this remarkable change is a small one. It involves the cortex in the depth of the posterior part of the superior limb of the arcuate sulcus (fig. 1). The approach to the tissue at the depth of the sulcus can be made from either bank, but the lower has

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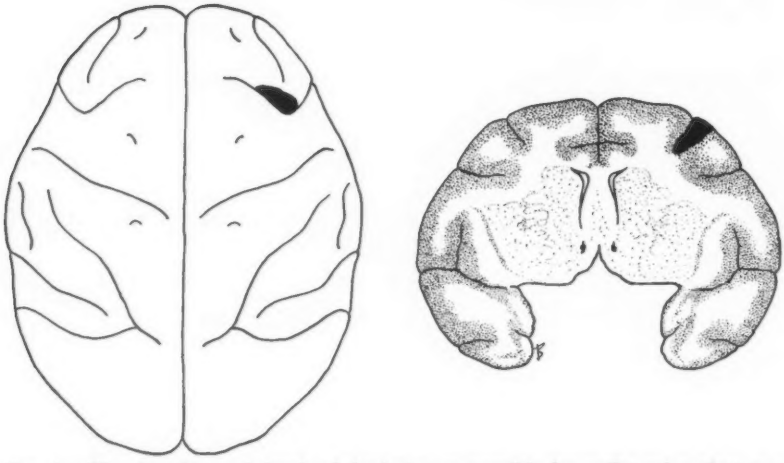

FIG. 1.—The situation and depth of the lesion responsible for unilateral neglect are shown.

almost invariably been chosen in these experiments. The amount of tissue which it is necessary to remove is less than half a gram.

The neglect is evident when the animal wakens from the anæsthetic, but it is best to wait for a day and examine the animal when recovery from operation and anæsthesia is more complete.

Then it will be observed that the animal tends to sit at the back of the cage, with the involved side of the body toward the examiner and toward the greater part of external space. There is spontaneous circling activity toward the side of the lesion, and when the animal is aroused the activity is increased. When attempts are made to catch the animal, the involved side is again most often presented to the examiner. The visual change can be tested with the animal held or free. With the attention of the animal engaged, and fixation of the animal's eyes on the examiner, objects can be brought into each visual field. When an object is brought from the uninvolved side, it is immediately observed that fixation changes to the object, and the object is frequently grasped or warded off. When the object is brought into the field on the involved side, it appears that no notice is taken of it until it is brought to about the vertical axis of the visual field, when there is an immediate and somewhat surprised response by the animal, in changing its fixation and grasping the object. When allowed to run at large, the animals sometimes collide with objects on the involved side.

The responses to auditory stimulation are less stereotyped in the monkey, but in an animal showing a fair amount of curiosity, auditory stimuli delivered outside the range of vision of the animal are followed

by turning toward the source of the stimulus and scanning of that area. Following the lesion described, auditory stimuli on the uninvolved side are very frequently productive of a turning toward the source of the stimulus and a scanning of that region. Auditory stimuli delivered in the involved half of space, however, very frequently result in a turning toward the wrong side and scanning of the uninvolved field for the source of the stimulus. This mislocalization of auditory stimuli occurs even after the impairment of head and eye turning has subsided to the extent that rotation of head and eyes is possible in either direction.

The irresponsiveness involves tactile stimuli as well. If the animal is touched or pricked with a pin outside his field of vision, or if a blindfolded animal is touched or pricked, there is usually an immediate rapid defensive reaction, with simultaneous withdrawal of the portion of the body touched, and an assault by the extremities upon the offending object. This normal response is seen when the uninvolved side of the animal is so stimulated. On the involved side, however, no notice seems to be taken, or if there is a response it is considerably delayed and rather indifferent in its performance.

The irresponsiveness to tactile stimulation seems most marked on the trunk, and least marked on the face, especially in the perioral region.

Stimuli of a more complicated sort have been tried: food, such as a carrot, a raisin, or some other attractive article, placed into the uninvolved side of the mouth is ordinarily taken with apparent relish, without very much delay. When the food is placed in the involved side of the mouth, there is ordinarily considerable delay, and if it is taken at all it is taken, again, in a rather indifferent manner. A jet of sugar-water directed against the upper lip of a blindfolded animal results in an immediate licking movement, when this is done on the uninvolved side. On the affected side, again there is usually a delay before the licking movements are initiated, and these are done less rapidly and consistently.

In one animal, peanut butter was smeared on the animal's lips on both sides, and he licked and ate the peanut butter from the uninvolved side, leaving the involved side smeared, reminiscent again of a situation not infrequently seen in patients showing unilateral neglect.

In the motor sphere, there is a disability of the extremity on the affected side, best characterized as a poverty of movement. In walking and climbing, the extremities are used well, but not with the dexterity shown by their opposite numbers. In activities requiring the use of only one hand, the uninvolved hand is ordinarily used, as the other rests quietly by the animal's side. It is of interest, however, that from time to time the involved extremity is used to ward off stimuli on the uninvolved side, usually in concert with the arm on the uninvolved side, but it is more

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frequent for the uninvolved arm to cross the mid-line for various activities than for the involved one to do so.

The tactile placing reactions are abolished or severely impaired on the affected side, and, as one would expect, if the table top is kept in the involved visual field the visual placing reactions are similarly impaired.

All these changes are transient, and recovery, which begins in five to seven days, seems complete in two weeks.

The abnormalities in response to touch and sound on the side opposite to a frontal lesion were observed in one animal previously rendered blind by bilateral occipital lobectomy.

When an effective frontal lesion on one side is added to occipital lobectomy on the other, the animal exhibits relative indifference to tactile and auditory stimuli on the side contralateral to the frontal injury, but behaves as though able to see. When visual testing is carried out, the animal's fixation of gaze can be engaged. Under these circumstances a moving object brought into the field of vision causes no response until it reaches the fixation area, when a brisk startle reaction ensues.

The unilateral neglect which has been described has not been seen following various other lesions of the cortex made during the course of these and other experiments. Superficial excisions which do not extend to the depth of the arcuate sulcus or injuries which do not involve the posterior part of the cortex at the depth of this sulcus are not effective.

The hemianopsia which follows occipital lobectomy is unaccompanied by changes in response to auditory or tactile stimuli, and animals with this deficit show no evidence of unilateral spatial neglect. Instead, by consistently scanning their environment by head, eye, and trunk movements, they effectively compensate for the defect which has been imposed.

Discussion

Although Hitzig (1884) had observed in dogs that following anterior hemispheral lesions there was transient loss of vision in the contralateral eye, together with an impairment of movement of the opposite extremities and intellectual loss, it was Bianchi (1895) who first clearly called attention to a contralateral perceptive defect after excision of the frontal lobe in monkeys and dogs. He described rotatory movements toward the side of the lesion, paresis of the opposite arm not evident in associated movement but obvious in more delicate movements, and a visual disturbance which had the characteristics of a contralateral hemianopsia. Tactile sensibility was described as normal, excepting for hyperæsthesia in the opposite ear and face in one monkey. In another, he found diminished hearing on the affected side. Bianchi was more concerned with an analysis of the total deficit following frontal lobe injury than with the apparent hemianopsia which he discovered. It is difficult to know to what extent his observation of the perceptive deficit on the opposite

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side influenced the synthesis of frontal lobe function which he formulated: "Overlooking the possible contention of some objectors that the serious mental disturbances observed in the mutilated animals depend on interference with the sense of taste and smell, my hypothesis is that the frontal lobes are the seat of co-ordination and fusion of the incoming and outgoing products of the several sensory and motor areas of the cortex. As the nervous waves from peripheral organs of reception (retinal rods, tactile organs, and so forth) are transmitted from neurons of the first order to neurons of the second (mesencephalon, thalamus) and from these again to neurons of the third order (cortex) thus we may suppose that from the last-mentioned nerve impulses travel to the frontal neurons of the highest order. The frontal lobes would thus sum up into series the products of the sensory motor regions as well as the emotive states which accompany all the perceptions, the fusions of which constitutes what has been called the *psychical tone* of the individual. Removal of the frontal lobes does not so much interfere with the perceptions taken singly as it does disaggregate the personality and incapacitate for serializing and synthesizing groups of representations."

In adding to observations previously made by Ferrier, Ferrier and Turner (1898) observed, after frontal lobectomy in one monkey, a contralateral homonymous hemianopsia, together with impairment of tactile sensibility on the affected side. In another animal, following a combined lesion of the frontal lobe and posterior parietal region, anæsthesia of the opposite side was associated with the visual defect. This loss of cutaneous sensitivity, which was later mentioned by Kennard (1939), contrasts with the hyperæsthesia of the side of the face opposite the lesion observed by Bianchi. Ferrier and Turner considered that these symptoms might be explained by a "dynamic influence exerted by the magnitude of the lesion on the sensory centres or tracts which were not organically injured." It is interesting that an explanation involving diaschesis should have been offered, in view of the construction which Ferrier had previously made of the deficit from frontal lobe removal, that this defect was in the "faculty of attention" (Ferrier, 1886).

That a small lesion, confined to the cortex within the bend of the arcuate sulcus, is followed by all the changes which had hitherto been found with frontal lobectomy was shown by Kennard and Ectors (1938). They speculated about the nature of the disturbance in response to visual stimuli, and found it difficult to explain. They pointed out that the apparent perceptual defect could not be based upon impairment of head and eye movements, because it outlasted the disturbance in these by some little time. They proposed that the visual defect was more a disregard than a true hemianopsia, since the defect was transient and when the lesion was made bilaterally blindness did not ensue.

One year later, Kennard (1939) found the visual impairment following

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restricted lesions of the frontal lobe to be indistinguishable from a hemianopsia following occipital lobectomy. She described impairment of movement in the contralateral hand, characterized by relative disuse or incomplete and ineffective use without actual paresis, and considered the perceptive defect to be an apparent lack of recognition of objects, due to disturbance of complex integrative processes of the frontal lobe. Although Kennard was convinced that lesions restricted to the grey matter were capable of producing the syndrome, Clark and Lashley (1947) felt that injury to the subjacent white matter was important. They suggested that "the visual defect represented a traumatic disorganization of re-entry circuits producing interaction between frontal and occipital regions."

How vision, hearing, tactile sensibility, movement, and placing reactions are so seriously impaired by a lesion of the cortex which does not directly interfere with any of the several receiving areas or the motor area of the cortex is difficult to understand. The various hypotheses which presume interference with complex integrative functions dependent upon the area destroyed have in common several serious weaknesses. The first of these is that the specific functions or events which are supposed lost are rarely specifically defined in physiological terms, or, if defined, are stated in such a way as to be untestable by experiment or observation. The second objection is based on the observation that removal of such a small volume of cortex is capable of producing these profound effects. It is difficult to conceive that the essential neural basis for complex synthesis or integration involving movement and all aspects of sensation on one side could be contained in such a small volume of grey matter. We are led, therefore, to believe that it must be a rather simple event which is upset, and to suggest that this might be a facilitatory mechanism bearing upon the several receiving areas of the involved hemisphere.

Summary

Following a restricted lesion of the frontal lobe in the monkey, there is an impairment of response to stimuli of various sorts on the opposite side of the body and in the opposite half of space, accompanied by relative poverty of movement of the extremities on the affected side. Fragments of this disorder have been described in the past (Bianchi, 1895; Ferrier and Turner, 1898; Kennard and Ectors, 1938), the visual and motor symptoms having received attention.

The lesion responsible for this change is small (less than 0·5 gramme of tissue) and involves the cortex in the depth of the posterior part of the superior limb of the arcuate sulcus.

The change is a temporary one, the irresponsiveness involving all sensory modalities which can be tested. The impairment in response to visual stimuli resembles an homonymous hemianopsia, and is more

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marked in the peripheral field. Responses to auditory stimuli in the affected half of space indicate a mislocalization of the source of the stimulus in that it is referred to the unaffected side. There is relative disregard of tactile stimuli on the affected side, the impairment being least severe in the perioral region and face, and most severe on the trunk. Tactile placing reactions on the affected side are lost or severely impaired, and there is relative disuse of the extremities.

The mechanisms which are disturbed in experimentally produced neglect appear to be of a simple order, and may be facilitatory influences bearing upon the several receiving areas of the involved hemisphere,

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THE RELATIONSHIP BETWEEN CORTICAL AND PERIPHERAL EFFECTS OF CEREBELLAR STIMULATION IN THE CAT

BY

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WALKER'S experiments (1938) have shown that faradic stimulation of the cerebellar hemispheres brings about an increase in amplitude and frequency of the electrical potentials, especially in the cortical motor areas, bearing out the much earlier findings of Rossi (1912) on the dynamic influence of the cerebellum on the cerebral cortex. Analogous observations upon the desynchronization of the cerebral rhythms, activated and accelerated by stimulation of the cerebellum were furnished by Clark and Ward (1949) and by Alexanian and Firsov (1949). Cooke and Snider (1953) demonstrated an increase in the frequency of cortical rhythms due to cerebellar stimulation, not only in the motor areas, but also in the sensory areas.

In continuing our earlier investigations upon the influence of the cerebellum upon the excitability of the cortex (Kreindler and Steriade, 1957; Steriade, 1957), we studied the influence of cerebellar stimulation, not only upon cortical electrical activity, but also upon the state of the muscles, to see if any correlation existed between these two effects. This study aimed at establishing a relationship between the cerebellocortical and the cerebellospinal circuits.

METHOD

Under ether anæsthesia electrodes were introduced through the calvaria of 29 cats into different cortical regions as well as into different cerebellar lobules. The bipolar electrodes consisted of a pair of wires of 150 microns diameter, insulated except at the tip, giving focal cerebellar excitation and cortical recordings. The tips of the electrodes were half a millimetre apart. Under these experimental conditions, diffusion of the current into the neighbouring structures was minimal. The investigations were started one hour after the animal awoke from anæsthesia.

By means of a Schwarzer electroencephalograph with 8 channels, the electrocorticogram of the various cortical areas was recorded as well as the electrocerebellogram of the stimulated point and the electromyogram of the flexors and extensors of the fore-limbs, homo- and heterolateral to the stimulated cerebellar point. The

cerebellum was stimulated by means of a sinusoidal current of 50 Hz., the intensity of which was increased progressively, of 5 seconds' duration. The intensity of the stimulations varied for the weak ones between 0·7–1 mA. and between 1·5–2 mA. for the strong ones. It was necessary to use such a big milliamperage because of the high resistance due to the small diameter of the electrodes (150 microns) and the small distance existing between the tips of the electrodes.

After the experiment, the cat's head was fixed in formalin and the brain was sectioned parallel with the plane of the electrodes, to determine macroscopically the position of the electrode tip.

Results

Electrical stimulation of the neocerebellar structures (the anso-paramedian lobe, tuber and folium) induced a slight tonic contraction towards the stimulated part during the stimulation period, superimposed on some clonic spasms and a flexor contraction of the homolateral fore-limb, when the ansatus lobule was stimulated. In most cases, after cessation of stimulation, a prolonged after-discharge could be seen in the homolateral flexors which, with strong stimulation would even last for several minutes. Out of 16 animals studied, in only 3 cases could a contraction of the heterolateral flexor muscles be observed, while in two instances no effect whatsoever was observed in the homolateral flexors. Sometimes an inhibition of the heterolateral flexors could be noticed.

In 15 out of the 16 cases desynchronization of the electrocortico-graphic tracings was observed recorded from the convolutions of the area rostralis, genualis, præsplenialis, splenialis, fornicatus, sygmoideus, lateralis and suprasylvius medius. The desynchronization of the electrocorticogram consists of flattening of the records (fall in the amplitude of the waves from 50–70 μV to 20–30 μV.) and rise in frequency (from 6–11 c/s to 16–20 c/s). In general, desynchronization involves all cortical areas investigated, lower intensities of stimulation affecting more especially the cortical points heterolaterally to the stimulated cerebellar point, while higher intensities affected both hetero- and the homolateral points. We must point out that this very marked "arousal reaction" could be seen particularly while the records before stimulation constituted resting activity, represented by alpha rhythms of 8–9 c/s and theta rhythms of 5–7 c/s, whose amplitude ranged from 50 to 70 μV. With stimulation of equal intensity and duration, however, applied against a ground of "spontaneously" desynchronized cortical electric activity, the cortical effect could no longer be seen although the increase in muscular tone was just as great (figs. 1 and 2).

What seems important to us is that at low intensities of stimulation one may see the after-discharge either through cortical desynchronization alone, or through a longer duration of contraction compared with the homolateral flexor tone (36 seconds compared with 10 seconds, for instance, in one of the cats; fig. 3). On the other hand, at great

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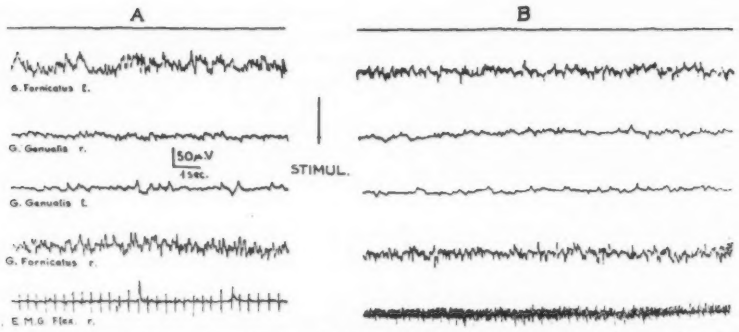

FIG. 1.—A, Prior to stimulation of the cerebellum, synchronous electrical activity at all points, formed by waves of the alpha and theta bands, with an amplitude of up to 100 μV; the electromyogram of the flexors of the right fore-paw shows resting activity. B, after stimulation of the uvula (right half) there is increase in tone of the flexors and general desynchronization of the electrocorticogram from the anterior and posterior cortical areas, hetero- and homolateral to the stimulated cerebellar point.

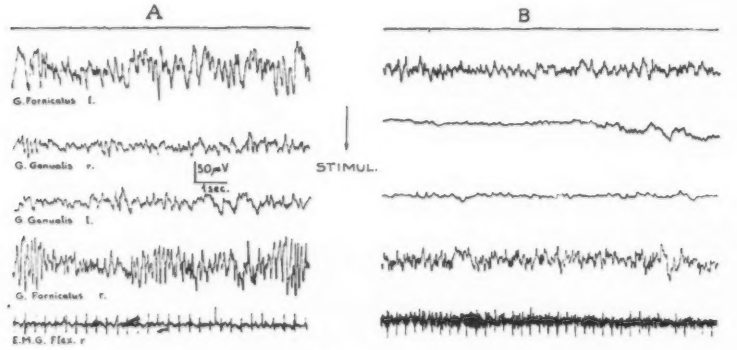

FIG. 2.—A, Prior to stimulation of the cerebellum, the cortical electric activity is desynchronized; muscular tonus at rest. B, After stimulation of the same cerebellar point (uvula, to the right) there is increase in tone of the flexors and some desynchronization, of records from the left gyrus fornicatus, the only point where prior to stimulation alpha waves had been observed.

intensities, the electrical stimulation of the cerebellum causes a much greater after-effect in the tonus of the flexors than in the electrocorticogram (for instance, in the same cat, 100 seconds in the tonic contraction against 68 seconds in the electrocorticogram); in this case, the synchronous rhythms of cortical rest reappear long before muscular relaxation (fig. 4).

The tonic contraction of the homolateral flexors as well as the

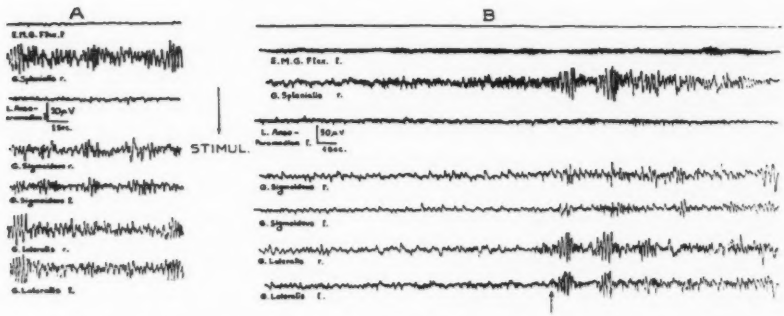

FIG. 3.—A, Prior to stimulation of the cerebellum, the synchronous activity in all cortical derivations is formed of waves of the alpha and theta bands, the electromyogram of the flexors of the left front limb show resting activity. B, After weak stimulation (1 mA., 5 sec.) of the left ansoparamedian lobe, no effect is seen in the muscle tone, despite the fact that cortical electric activity is desynchronized at all points, i.e. anterior, and posterior, hetero- and homolateral; at a given moment, the synchronous electrical activity reappears.

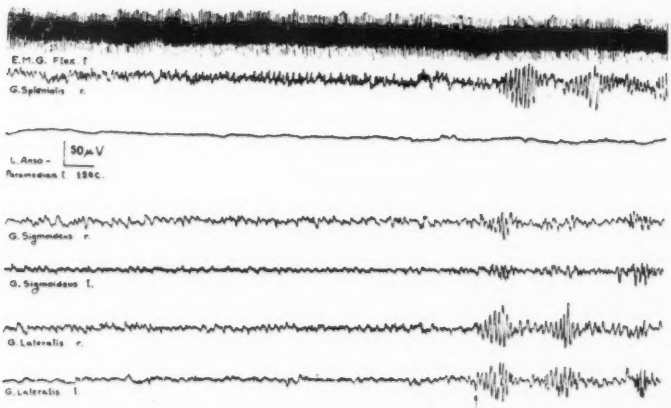

FIG. 4.—After a more intensive stimulation of the same point of the left anso-paramedian lobe (1·8 mA., 5 sec.), there is intense contraction of the homolateral flexor muscles which persists even after the cortical desynchronized activity has returned to its previous resting state.

desynchronization of the electrocorticographic tracing have appeared with much greater regularity on stimulation of the neocerebellar structures (anso-paramedian lobe), than of the vermis (tuber and folium), where the after-effect was not observed in all cortical points investigated and with all intensities of stimulation. At the same time, in some cases stimulation of the hemispheric structures (for instance, crus I) induces a greater homolateral flexor contraction than stimulation of the vermis (tuber).

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Stimulation of the paleocerebellar structures (lingula, centralis, culmen, pyramis and uvula) generally causes in our experimental conditions, the same type of response in muscle tone and in the cerebral cortex as the type of response caused by stimulation of the neocerebellum. Yet, stimulation of the paleocerebellum does not cause the same constancy of response and other forms of reaction are also met, such as for instance increase in muscle tone without cortical response, or inhibition of tone with cortical desynchronization.

In 10 per cent of cases we observed slow waves (3–7 c/s), appearing especially in præsplenial and homolateral splenial points (both on stimulation of the neocerebellum and of the paleocerebellum), lasting for a few seconds after cessation of the stimulation.

Discussion

These experiments show in the first place that electrical stimulation of the cerebellum causes electrical activation of almost all cortical areas, motor and sensory, homo- and heterolateral, in the form of a marked "arousal reaction," consisting in desynchronization of the cortical rhythms, with increase in the frequency of the waves and the marked decrease in their amplitude. The experiments of Walker (1938) in the "encéphale isolé" of the cat likewise demonstrated that stimulation of the cerebellar hemispheres induces a cortical bio-electric activation, which was seen especially in the contralateral motor cortex and disappeared after section of the superior cerebellar peduncle, which allows the inference that there exists a transmission of the cerebellifugal discharges along the known connexions, the cerebello-dento-rubro-thalamo-cortical pathway. Our investigations, which show a generalized activation of the cortical electrical activity through stimulation of the cerebellum, make us believe that the influence of the cerebellum on the excitability of cerebral cortex is exerted not only through the pathways mentioned, but also by a diffuse and bilateral projection, probably the cerebello-reticulo-cortical connexions. The rôle of the reticular formation of the brain-stem in the transmission of the cerebellifugal discharges (Snider, McCulloch and Magoun, 1949; Mollica, Moruzzi and Naquet, 1953), as well as the activating action of these structures upon the cerebral cortex (Moruzzi and Magoun, 1949; Magoun, 1952) may justify this hypothesis.

Our investigations also suggest that stimulation of the cerebellum may cause an arousal reaction almost invariably against a background of synchronous cortical electrical activity, the influence of the cerebellum on the cerebral cortex becoming less evident as cortical electrical activity becomes more desynchronized. This suggests that the influence of the cerebellum on the cortex depends on the functional state of the cerebrum. Moreover, in this respect, our electroencephalographic data agree with

those of Moruzzi (1941) who showed that paleocerebellar excitation has different effects depending upon the functional state of the sigmoid gyrus.

The fact that weaker stimulation of the cerebellum induces the desynchronization of the electrocorticographic tracing without influencing muscular tone, demonstrates that the threshold of the cortical electrical response to stimulation of the cerebellum is slower than that of the muscle tone. At the same time the fact that the muscular after-effect continues longer than the cortical after-effect, at greater stimulation intensities, constitutes an additional argument in favour of the existence of cerebellospinal circuits that are entirely independent of the cerebellocortical circuits.

The complexity and the great variability of responses elicited through stimulation of the peleocerebellar medial structures may be explained by the intricacy at this level of elements having differing functional status, for instance spinal, cortical or vestibular.

Summary

(1) The relation between the cortical and peripheral effects of cerebellar stimulation in the cat have been studied, with simultaneous electrocorticograms of the various areas, electrocerebellograms and electromyograms. Stimulation of the neocerebellar and paleocerebellar structures causes an increase in tone of the flexor muscles, with a homolateral predominance, and a generalized desynchronization of the cortical rhythms in the form of "arousal reaction."

(2) At low intensities of stimulation, desynchronization without change in tone may be observed, suggesting that the threshold of the cortical effect is lower than that of the peripheral phenomenon. Greater intensities of stimulation cause a longer duration of the activation in the electromyogram than of cortical desynchronization, constituting an additional argument in favour of the existence of cerebellospinal circuits that are entirely independent of the cerebellocortical ones.

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OBSERVATIONS ON THE BLOOD VESSELS OF THE SPINAL CORD AND THEIR RESPONSES TO MOTOR ACTIVITY

BY

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(1) INTRODUCTION

IT is a well-known principle of physiology that as the metabolic rate of an organ increases with activity it is accompanied by local vasodilatation and an increased blood flow. This has been demonstrated in the secreting submandibular gland by Claude Bernard (1858) and by Barcroft (1908), in striated muscle by Krogh (1919), in cardiac muscle by Green and Gregg (1940) and in the stomach by Wolf and Wolff (1943). Leonard Hill (1896) first suggested that there was a relationship between brain metabolism and its blood flow and this was further supported by the observations of Fulton (1928) on a patient with an occipital angioma. The animal experiments of Cobb and Talbott (1927), Serota and Gerard (1938) confirmed the thesis that nerve-cell activity in the cerebral cortex is accompanied by a local increased blood flow. Many years previously Gowers (1899) inferred such a relationship in the spinal circulation. He says: "An active congestion, which may be called secondary, seems to result from prolonged and violent action of the nerve elements of the spinal cord. Thus local vasodilatation and distension of vessels, migration of leucocytes into the sheath and into adjacent tissue, and even small extravasations are found in some cases of hydrophobia, of tetanus and of strychnine poisoning, and it is probable that a similar congestion attends all violent physiological activity, violent and continued exercise, coitus, etc. Coitus several times repeated has been known to cause hæmorrhage within the cord which must be accompanied by intense congestion. Vascular dilatation, with an increased blood supply, is the physiological attendant of functional activity in all organs and doubtless also in the cord, but it is morbid only when excessive."

More recently Trueta and Hodes (1954) have shown that extensive hæmorrhage in the lumbar region of the spinal cord may result from

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the injection of highly irritant substances (such as 10 per cent formol saline or croton oil) into the thighs of mice. They also indicated that intense hyperæmia of the lumbar cord accompanied swimming to exhaustion.

During the last seventy years an extensive study of the comparative anatomy of the spinal blood vessels in a wide range of vertebrates, including man, has revealed a complex but more or less homologous pattern of supply and drainage (Kadyi, 1889; Sterzi, 1904; Hoskins, 1914; Tureen, 1936; and Bolton, 1939), and the syndromes resulting from major lesions of this vascular tree are well known (Marinesco, 1896; Spiller, 1909; Tureen, 1938). On the other hand, adaptation of the spinal circulation to increased nervous activity has received little attention, presumably due to great technical difficulties, though an understanding of its physiology may throw light on the pathogenesis and localization of certain diseases of the spinal cord. While the circulation in the pia mater and deeper structures of the cerebral hemispheres has been observed and studied during the last thirty years, the same experimental methods are hardly applicable to the spinal circulation. Changes in cerebral circulation with nervous activity have been noted by measuring the blood flow in an internal jugular vein using a heated thermocouple (Gibbs, Gibbs and Lennox, 1935) or by the nitrous oxide modification of Fick's principle (Kety and Schmidt, 1945), techniques which are applicable because of the relative simplicity of the vascular hilum of the brain and from which one can deduce the blood flow in absolute values, i.e. millilitres per minute per 100 grammes of tissue. Unfortunately such methods are impracticable in the case of the spinal cord which draws its arterial supply from many different levels and returns its venous blood in an equally complex manner.

The heated needle thermocouple has also been placed within the brain to register changes of local blood flow, but the hæmodynamic equilibrium of the cord may be upset by the laminectomy which would have to be done to insert the thermocouple, and the latter, by its mere presence in such a compact structure as the spinal cord, may interfere with its function. Nevertheless, in spite of these theoretical objections, Field *et al.* (1951) have used this method to record changes of blood flow in the exposed and cooled spinal cord of rabbits, and under these conditions stimulation of the sciatic nerve was accompanied by an increased spinal blood flow limited to those segments of the cord from which the sciatic nerve arises.

Histological methods provide only a static picture of the blood vessels at the time of fixation, but the dilatation and opening up of blood vessels that occurred during life can be recognized histologically and more obviously when "normal" vessels are also present in the section. Indeed, the blood vessel dilatation and increased blood flow that occur in early inflammation are reflected histologically as well as functionally. It seemed reasonable therefore, to study changes in the cord circulation

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as a result of activity by this method, provided that it could be compared with an identical region that had not been so activated. By choosing the spinal flexor reflex elicited by single shocks to one hind-limb in an anæsthetized animal, it has been possible to compare the size and density of the blood vessels on the two sides of the cord and to relate these changes to the motor activity.

(2) Methods

33 young brown mice each weighing about 25 grammes were used in this study. They were lightly anæsthetized by an intraperitoneal injection of chloralose (4 mg./100 grammes) and urethane (50 mg./100 grammes) dissolved in normal saline. They were supported in groups of 4 or 5 on a net hammock through which the hind-legs protruded and the abdomen rested on a metal strip covered in saline-soaked gauze which formed the positive pole of the stimulating circuit. The hind-limb selected for stimulation had fine copper wire wound round the toes and a 10 grammes brass weight was suspended from this, making contact with a bowl of saline placed under the hammock. This formed the negative pole of the stimulating circuit. 30 msec. "square wave" pulses were employed at 2-second intervals and the least voltage required to produce leg flexion and lifting of the weight, was determined for each batch of mice. In this way, crossed extensor and other associated reflexes were avoided. 4 mice were usually connected in this manner; the fifth was insulated from the positive electrode and thus acted as control. Stimulation was continued for half to two hours when the animal was removed from the hammock, the heart rapidly exposed, a cannula inserted into the left ventricle and perfusion commenced with 0·9 per cent saline at 37° C. at 5 ft. pressure of saline. This was continued until the effluent from a small cut in the right side of the heart was clear, when indian ink (Günther Wagner; diluted 1 in 4 with saline) was substituted for the saline at the same pressure and temperature. When injection was complete (as judged by the appearance of viscera and especially skin), the skin along the whole of the back was incised and the animal fixed in 10 per cent formol saline. Twelve hours later the whole of the vertebral column could be dissected away from the corpse without leakage of injection material. The activated side was marked by drawing a line in indian ink along the whole length of the vertebral column. Fixation was continued in 10 per cent formol saline for about another fourteen days when the material was decalcified in a mixture of formic acid (25 per cent) and formaldehyde (10 per cent) and then dehydrated, cleared and blocked in paraffin. Sections were cut at 30 μ and 100 μ and every fifth serial section was mounted and examined unstained.

(3) Assessment of Results

A suitable quantitative method of assessing this type of material has been sought. Craigie (1920 onwards) measured the length of capillaries in a known volume of tissue and his comparison of the relative vascularization of areas of the C.N.S. is based on this. We were looking not only for increased vascularization but also blood vessel dilatation. We have therefore assessed each section qualitatively, scoring +1 for greater number of blood vessels on the activated side and +2 if dilatation is also present. If both sides of the cord appeared to have an equal number of blood vessels, 0 was scored. Similarly, if it should happen that a greater number of vessels was visible on the non-activated side, −1 was scored

and should dilatation of these blood vessels also be apparent —2 was scored. Each series of sections was examined and assessed by two observers working independently and separate score cards kept. In the case of the control experiments the spinal columns had been marked along the whole of the right side and identical scoring was undertaken for these. At the time of assessing these sections, the observers did not know which were from control animals and which were from the exercised group. This has shown a small but definite observer preference for scoring pluses, which nevertheless has not obscured the main result of this work. No attempt has been made to assess sections which were imperfect, oblique or torn.

The individual results of both observers were remarkably consistent but minor disagreements did occur over individual sections and these were then re-submitted to examination, re-assessment and, if necessary, discussion.

(4) Results

It was convenient to mount twelve sections on each slide, six for example from the lumbar region and six from the cervical. If the total scores of each group of six sections are plotted as ordinates against anatomical levels as abscissæ, a graph is obtained which shows up any region of excessive vascularity on one side of the spinal cord as compared with the other. In fig. 1A which has been plotted from a control animal there is a more or less random scattering of scores with a small preference for positive scoring, i.e. for considering the marked side of the spinal cord to have a greater density of blood vessels. However, no very definite pattern emerges, which is in striking contrast to graphs prepared from the exercised animals, of which fig. 1B is an example. Here there is a well-defined maximum in the lumbar region extending into the sacral segments of the mouse cord. This suggests that vascular dilatation and

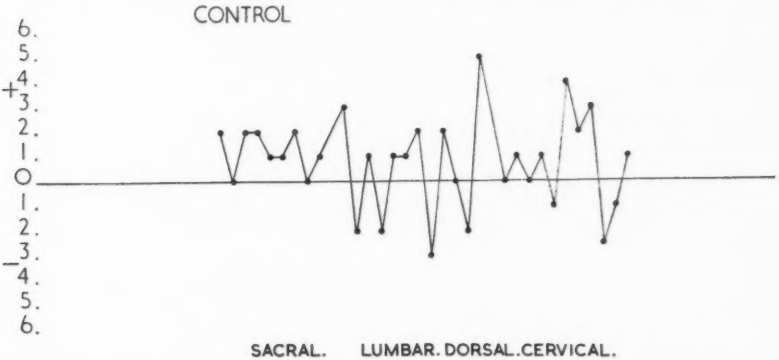

Fig. 1A

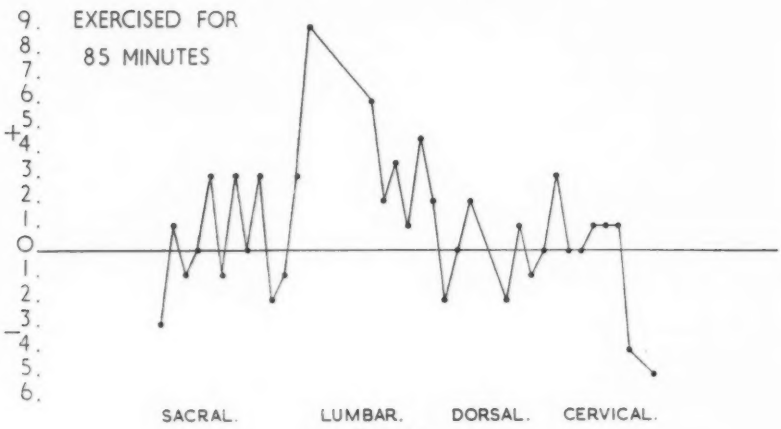

FIG. 1B

FIG. 1.—Graphs to show distribution of vascularity in the spinal cord, plotted (A) from a control animal, and (B) from an animal exercised for 85 minutes. The whole cord is sectioned at 30 μ and each section is scored +1 for increased number of blood vessels, and +2 if dilatation is also present on stimulated side; conversely −1 and −2 is scored if increased number and dilatation occur on non-stimulated side. The total score for one series of 6 sections is plotted as an ordinate, against the anatomical level as an abscissa.

increased density of blood vessels is localized to the homolateral region of the spinal cord segments activated, in this case, by the spinal flexor reflex in a single lower limb.

Of 33 animals, 7 acted as controls and 5 were incompletely injected. 16 of the remaining 21 mice gave typical results, and in 5 animals there was dilatation of blood vessels in patches only of the lumbar and sacral cord, but also extending into thoracic segments.

We have been unable to demonstrate any simple relationship between duration of exercise and the vascular response. In the cords of mice exercised for 30 minutes the increased density and dilatation of blood vessels on the homolateral side has been sometimes as intense as in mice exercised for much longer periods up to 105 minutes.

Transverse sections of the spinal cord show in both control and exercised groups a much better filling of the blood vessels of the lumbar cord with the perfusion material than those of the cervical region (fig. 2, Plate XLIX). As perfusion was performed from the left side of the heart, this difference in observed vascularity would seem to be not an artefact of the method. On the whole, the lumbar cords of the control group of mice show an even distribution of blood vessels on the two sides of the spinal cord. In contrast to this, lumbar cords from the exercised groups show a relative

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increase in blood vessel density and often wide dilatation on the ipsilateral side of the cord (figs. 3 and 4), a state of affairs persisting over many serial sections. Blood vessels entering the cord from the spinal roots are often particularly prominent on the same side as the exercised limb and other extramedullary vessels are also often widely dilated.

In thick sections of the spinal cord (100 μ) an identical state is found, but of course the capillary network is more clearly visualized (fig. 4). This must mean that during periods of inactivity some blood vessels of the spinal cord are not patent but become so only when the cord is excited to greater activity (cf. Krogh, 1919).

During this study we have confirmed the importance of penetrating coronal vessels in supplying blood to the anterior portion of the spinal cord (fig. 5A). The coronal vessels are part of an anastomotic network formed by branches of segmental lumbar vessels gaining access to the pial surface of the cord accompanying the nerve roots. The anterior spinal artery in this region probably derives most of its blood supply from the thoracic portion of the same artery, and is augmented by spinal vessels arising from the lumbar arteries (Bolton, 1939). Occasionally transverse sections have demonstrated the extent and distribution of the anterior spinal artery in both lumbar and cervical segments of the cord. In both these regions its distribution tends to be limited to the medial grey matter of the cord with sparing of the dorsal columns (figs. 4A and 5B). Often, even in thick sections, the anterior spinal artery in the lumbar region was very small and penetrating branches of the coronal vessels supplied virtually the whole of the anterior portion of the spinal cord. There was, however, a great deal of individual variation from one animal to another and such an inconstancy of the anatomy of the spinal circulation has been described previously for many other mammals including man (Tureen, 1938).

(5) Discussion

A. Blood Vessel Adaptation to Nervous Function

In our experiments, blood vessel dilatation and opening up of capillaries within a fairly localized region of the spinal cord, occurred when a single hind-limb performed work by flexing against a small resistance. Thus the circulation of the spinal cord behaves in a manner which we can now call typical of any actively working organ.

We have no experimental observations on how the blood vessel changes are initiated, whether reflexly or directly by the action of local metabolites from activated nerve cells. The pial vessels of the spinal cord are supplied by fine unmyelinated nerve fibres even down to the capillaries (Stöhr, 1932). These reach the pia through the perivascular sympathetic plexuses and possibly also the dorsal roots. Clark (1929) was able to show that the ntrinsic arteries of the cord were supplied with very fine unmyelinatedi

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nerve fibres which turned in from the pial vessels. No nerve fibres to either capillaries or veins were demonstrated, but we must note that intrinsic blood vessel innervation of the brain even, is technically difficult to demonstrate (Penfield, 1932). Thus, a possible efferent pathway of a reflex arc to bring about an increase of the intrinsic spinal circulation has not so far been adequately demonstrated.

On the afferent side, the sensory influx was the result of stimulating nerve-endings in the skin of the toes and proprioceptive endings in the muscles. During the flexion reflex against the resistance, discharge of Golgi endings within the flexors and muscle spindles within the extensors, could possibly have far-reaching reflex effects which might include vasomotor phenomena within the cord. In the cerebral circulation, Cobb (1932) favoured the idea that local metabolites from active nerve cells caused a local blood vessel dilatation and increased blood flow. It is certainly known that one of these metabolites, carbon dioxide, has intense vasodilator properties.

B. Clinical Implications

(i) *Intermittent Claudication of the Spinal Cord*

In 1911, Dejerine fully described this interesting condition and discussed the clear differentiation from peripheral vascular diseases of the affected limbs and from muscular disorders. Characteristically, the patient complained of heaviness (but not pain) and weakness of both lower limbs coming on and progressing in intensity during walking and recovering on resting. The whole sequence was repeatable on resuming activity. Such a patient had no signs of vascular abnormality in the lower limbs, neurological signs of a mixed upper and lower motor neurone type were sometimes demonstrable immediately after exercise and usually completely reverted to normal after a period of rest. Sphincter trouble sometimes occurred and sooner or later a permanent paraplegia resulted. It is probable that most of Dejerine's patients suffered from neurosyphilis, but a similar syndrome due to arteriosclerosis has been described by Reichert *et al.* (1934).

It is to be expected that pathological medium-sized blood vessels, whether syphilitic or arteriosclerotic in origin, allow sufficient blood to reach the spinal cord to meet its metabolic needs at rest and for a limited amount of exercise. With further activity, however, the adaptive responses of these vessels being already partly or fully in action, cannot meet the increased cellular demands, resulting in a progressive partial anoxia of the cord, and recovering on rest when its oxygen debt has been cleared.

(ii) *Transient Symptoms in Multiple Sclerosis and Fluctuations in Spastic Paraplegia*

McAlpine *et al.* (1955) have described symptoms in multiple sclerosis which last a few minutes only. We cannot conceive of a pathological lesion

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such as œdema or gliosis, which could be as short lived as this. If, however, a lesion is already interfering with the blood vasculature of the cord, then an increased demand of the region involved during activity cannot be met and relative anoxia would result. Thus motor and sensory symptoms of brief duration might arise until the excessive metabolic needs have decreased again.

The improvement in spastic paraplegia after a limited amount of exercise and its worsening after undue fatigue is again suggestive of the influence of vascular factors acting on a neural mechanism that is balanced near the verge of anoxia. Increase of flexor spasms at night is a common complaint of the paraplegic patient, and we postulate the following mechanism: The blood flow to the spinal cord is lessened with inactivity, diminished cardiac output and redistribution of blood in sleep, and impairs still further the nerve pathways maintaining the spastic state, thereby tending to reduce this to the "spinal" state with its increased flexor tone. Revascularization of a diseased spinal cord by eliciting an inflammatory response to intrathecal tuberculin (Smith *et al.*, 1957) may help reduce the incidence of flexor spasms through this mechanism.

(iii) *Localization of Poliomyelitis*

It is now accepted (Bodian, 1954*a*) that in the preparalytic stage of poliomyelitis, viræmia is present. Before this was established, a number of provoking factors in the localization of the subsequent paralysis were known clinically, and various authors met great difficulty in trying to explain localization factors in terms of virus transmission along peripheral nerve pathways. Bodian (1954*b*) was able to deduce from his experiments a reflex effect of trauma on the permeability of spinal cord vessels and a possible relationship between this and the localization of the virus. Similarly a correlation between the site of prophylactic injections against diphtheria and whooping cough during presumptive poliomyelitis viræmia and the subsequent development of paralysis has been established (Medical Research Council Committee on Inoculation Procedures, 1956).

Russell (1947) showed that there was a relationship between the localization of the paralysis and the nature of severe exercise performed during the preparalytic stage of poliomyelitis. Buchthal (1949) also pointed out that in a large unselected series of cases of poliomyelitis the lower limbs were twice as frequently affected as the upper, and furthermore the muscles performing the greatest mechanical work, the quadriceps, anterior tibial and peroneal muscles in the lower limbs, the deltoid, biceps and triceps in the upper, were the ones most commonly affected.

It seems probable that localization of poliomyelitis by trauma and by exercise to the appropriate region of the spinal cord occurs because

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of the increased local vascularity of the cord, with dilatation and possibly an increased permeability of the blood vessels in the viræmic stage of the disease. We have been able to demonstrate that the increased vascularization of a local region of the spinal cord does accompany exercise of a limb in the mouse and these experiments could be extended further to show whether or not injected particulate matter or even virus more readily penetrated this region of increased blood flow.

(iv) *Miscellaneous Conditions*

It seems clear that neural tissue might have an adequate blood supply to maintain normal structure (as seen histologically) but inadequate for physiological function. The neurological deficit in cases of spastic paraplegia of undetermined ætiology (Marshall, 1955), Arnold Chiari malformation, basilar impression and cervical spondylosis (Mair and Druckman, 1953) might well be reconsidered in terms of underlying blood vessel disorder.

Summary

(1) Knowledge about the spinal circulation is reviewed.

(2) Experiments on the mouse are described which show that when a single hind-limb is exercised an increase in visible blood vessels with blood vessel dilatation occurs in a localized ipsilateral region of the cord.

(3) Physiological and clinical implications of these findings are discussed.

It is a pleasure to thank Mr. E. H. Leach and Mr. T. Marsland for the photomicrographs.

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FIG. 2A

FIG. 2B

FIG. 2.—Control experiment. 30 μ transverse sections of (A) cervical and (B) lumbar cord of mouse injected with indian ink to show blood vessels. (×70 in this and subsequent photomicrographs.)

To illustrate article by J. N. Blau and Geoffrey Rushworth.

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PLATE L

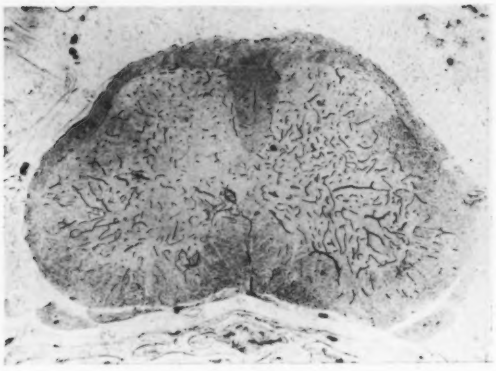

FIG. 3A

FIG. 3B

FIG. 3.—30 μ transverse sections of lumbar cord injected with indian ink to show blood vessels. In (A) the right hind-limb has been exercised for 30 minutes and shows an increased blood vessel density and dilatation restricted to the ipsilateral side; B, from another animal in which the left hind-limb has been exercised for 75 minutes. In regarding the vasculature of the two sides, the authors found it of help to compare the number and size of vessels in the anterior, lateral and posterior horns separately, before looking at the cord as a whole, which in addition shows a greater number of vessels in the white matter on the stimulated side.

To illustrate article by J. N. Blau and Geoffrey Rushworth.

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FIG. 4A

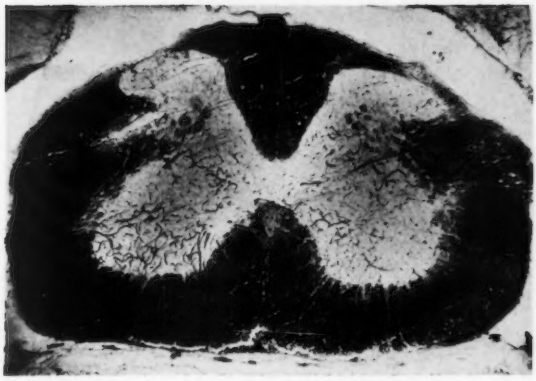

FIG. 4B

FIG. 4.—A, Section of upper lumbar cord 100 μ thick. From an animal that had its left hind-limb exercised for 45 minutes, showing increased number and size of small blood vessels especially in the anterior horn of the ipsilateral side; B, same animal, a more caudal section.

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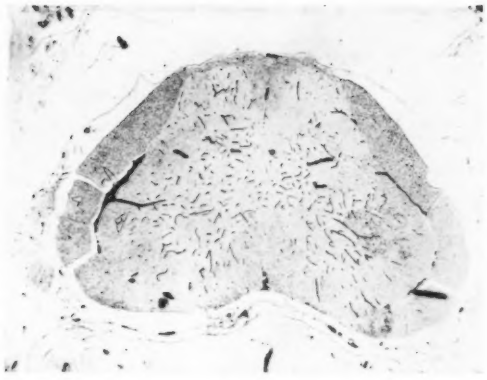

FIG. 5A

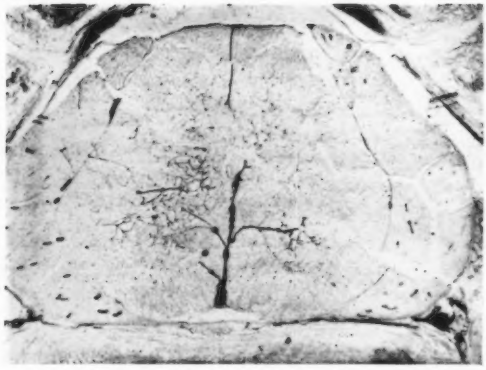

FIG. 5B

FIG. 5.—30 μ sections selected to show the blood supply of the lumbar region. A, the anterior spinal artery is very small but penetrating branches of the coronal network are prominent; B, the anterior spinal artery is large (this was from a mouse whose left hind-limb was exercised, also showing greater vascularization of the anterior horn and prominent vessels accompanying nerve roots).

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CORTICOBULBAR CONNEXIONS TO THE PONS AND LOWER BRAIN-STEM IN MAN

An Anatomical Study

BY

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I. Introduction

Ablation-degeneration studies reported earlier (Kuypers, 1956, 1958) revealed that in the cat the corticofugal fibres from the frontal parts of the hemisphere, including the motor cortex, were distributed mainly to the following areas in the pons and the lower brain-stem:

(*a*) The region ventral to and in the "hilus" of the nuclei cuneatus and gracilis, as well as the spinal trigeminal nucleus and the lateral parts of the tegmentum up to the level of the isthmus.

(*b*) The central part of the tegmentum of the medulla oblongata.

(*c*) The magnocellular division of the lateral reticular nucleus of the medulla.

(*d*) The tegmentum of the pons, especially on the ipsilateral side.

On the other hand, in this animal very few if any corticofugal fibres could be traced directly to the motor nuclei.

Furthermore, it was found (Kuypers, 1958) that in the cat the fibres from the motor cortex to the trigeminal complex and the lateral tegmentum originate mainly in the face area. The distribution area of these fibres constitutes the uninterrupted rostral continuation of the area of pyramidal termination in the spinal cord. According to Cajal (1909) and Lorente de No (1933), these cell groups in turn entertain numerous fibre connexions with the majority of the motor nuclei in the pons and lower brain-stem.

[1]From the Department of Anatomy, University of Maryland School of Medicine, Baltimore, Maryland, U.S.A. The early part of this work was carried on at the Department of Clinical Neurology, University of Groningen, Netherlands. A part of this study, together with the first results of the investigations in cats, were presented at the meeting of the American Association of Anatomists, Milwaukee, Wisconsin, U.S.A., on April 4, 1956. This investigation was supported in part by the research grant No. B 1131 from the Division of Neurological Diseases and Blindness of the U.S. Public Health Service.

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which is substantiated by the fact that lesions in this region are followed by a profuse terminal degeneration in the motor nuclei (Nauta and Kuypers, in the press). These observations suggested that in the cat such corticofugal fibres form the pathway by which the motor cortex influences the motor nuclei in the pons and medulla oblongata, through one or more synapses in the trigeminal complex and/or the lateral part of the tegmentum.

These earlier results were obtained by a study of nerve fibre degeneration in the brain-stem resulting from the removal of small parts of the motor cortex, using the selective silver impregnation method of Nauta and Gygax (1954). This technique reveals much more detail than the Marchi method, which by its very nature demonstrates degeneration of myelinated fibres only. Since these corticofugal connexions to the pons and lower brain-stem in man had, until the present time, never been studied with the silver techniques, and especially since none of the connexions found in the cat had previously been described, it was felt necessary to reinvestigate this problem in the human brain. The present report deals with such a study carried out on human pathological material.[1]

II. Materials and Methods

The pons and medulla oblongata were studied in four human brains in which was present either an encephalomalacia, resulting from an occlusion of the middle cerebral artery, or a hæmorrhage in the internal capsule. In all cases death had occurred within a period of two months after the onset of the symptoms.

Case 1.—Female, aged 79. The neurological case history reported an acute cerebrovascular accident on August 29, 1955, resulting in loss of speech and a hemiplegia on the left side. The patient was admitted to the hospital on September 30, 1955, where she died on October 4, 1955.

Brain autopsy revealed an almost complete obstruction of the stem of the right middle cerebral artery by an arteriosclerotic plaque and a softening in the supply area of the artery. Survival period after the cerebrovascular accident: thirty-six days.

Case 2.—Male, aged 67. The neurological case history reported that the patient complained about weakness and unsteadiness since September 1955. He had a cerebrovascular accident on December 3, 1955. After transfer to the hospital in a semi-comatose condition, he died on January 3, 1956.

Brain autopsy revealed a few old contusion foci in both orbital lobes and the left temporal lobe. In addition, an extensive encephalomalacia was found extending over the entire supply area of the middle cerebral artery. The process had probably been caused by an occlusion of the artery due to an arteriosclerotic plaque. Survival period after the cerebrovascular accident: thirty days.

[1]The human material used in this study was kindly made available by Dr. C. Lindenberg, Chief of the Neuropathological Service of the State Medical Examiner's Office in Baltimore, Maryland, as well as by Dr. J. Wagner, head of the division of Neuropathology of the University of Maryland School of Medicine in Baltimore, Maryland.

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Case 3.—Female, aged 66. The neurological case history reported that the patient, who suffered from hypertension and cardiac insufficiency, fell ill on October 13, 1956, with a weakness of the right side of the body. She became gradually confused and dysarthric. The patient was transferred to the hospital and died on October 21, 1956.

Brain autopsy revealed arteriosclerotic changes in the large brain vessels. Moreover, an extensive hæmorrhage was present in the left corpus striatum and the lateral thalamus which perforated through the angle of the lateral ventricle and extended down into the cerebral peduncle to the level of the mesencephalon. Survival period after the cerebrovascular accident: eight days.

Case 4.—Female, aged 78. This patient, who had a history of frequent spells of unconsciousness, was transferred to the hospital on April 28, 1956, with a paralysis of the upper extremity and aphasia, and died shortly after admission.

Brain autopsy revealed a fourth degree of arteriosclerosis with almost complete occlusion of the left carotid artery as well as of the frontal and parietal branches of the left middle cerebral artery. Moreover, a recent softening was found in the supply area of the frontal branches of the left anterior cerebral artery as well as a softening in the supply area of the middle cerebral artery. The exact survival period after the cerebrovascular accident in this case was not known.

After a fixation for fourteen days in 10 per cent neutral formaldehyde, the pons, medulla oblongata and upper part of the cervical spinal cord of all the brains were cut in frozen sections of 25 micra thickness. The brain-stem of Case 1 was cut in the transverse plane; the caudal part of the brain-stem of Case 2 was cut sagittally and the rostral part in the transverse plane; the brain-stem of Case 4 was cut entirely in sagittal sections. In Case 3 the caudal part of the brain-stem was cut sagittally in a plane oriented at an angle of 50 degrees with the median plane; the rostral part of the brain-stem was cut in transverse sections.

The sections were kept in 10 per cent neutral formaldehyde for a few months and then subsequently impregnated following Nauta and Gygax's (1954) selective silver impregnation technique.

It is a common experience that a satisfactory silver impregnation is difficult to obtain in human obduction material, as compared with animal material. The same holds true for the silver impregnation following the Nauta–Gygax (1954) technique. These differences are in all likelihood at least in part due to differences in the method of fixation of the tissue. In the experimental material, fixation is normally initiated simultaneously with death, by perfusion of the animals circulation with saline followed by the fixation fluid. On the other hand, in human material fixation is frequently initiated several hours after death. Moreover, it is regularly obtained by emersion of the tissue in the fixation fluid, rather than by perfusion.

The Nauta–Gygax silver impregnation technique, used in this study, consists of a Bielschowsky type impregnation, preceded by an oxydation-reduction pre-treatment. This silver method tends to promote a heavy impregnation of degenerating fibres and end-ramifications, while much less silver is deposited on the normal fibres. The contrast produced by this differential impregnation is in part a function of the overall intensity of the impregnation, which in turn can be controlled by means of the duration of the oxydation-reduction pre-treatment, and which must be adjusted to the needs of each individual brain. Such a "selective" impregnation among others facilitates the tracing of degenerating axons through a network of normal fibres, which was almost impossible in sections impregnated according to the classic silver impregnation techniques. However, it must be emphasized that although the heavier impregnation of degenerating elements aids in their detection, the diagnosis of degeneration must be

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based ultimately upon the pathologic morphology of the fibres characterized by local swelling, granulation, vacuolization and disintegration (Glees and Nauta, 1955). In other words, the mere fact of a heavier impregnation in itself can never justify the conclusion that the nervous elements are degenerating. This point is of especial importance, since some fibre systems tend to accumulate more silver than others, although the fibres are normal and by no means degenerating.

The present study covered six brains of which only four are reported here, since the other two could not be impregnated satisfactorily. Only pathologic material was used and no normal material was included. The demand for controls, however, was satisfied by comparing symmetrical structures, which receive degenerating elements unilaterally. In view of the commonly observed impregnation differences between two individual human brains, this offers the distinct advantage of comparing two structures in one section taken from one and the same brain. Some of the photographs which accompany this paper have been taken from bilaterally homologous regions; they will serve to illustrate the above-mentioned point.

III. Results

(*A*) *Pons, Medulla Oblongata and Upper Cervical Spinal Cord as Studied in Transverse Sections: Cases* 1 *and* 3

In the upper part of the cervical spinal cord (fig. 1 A), the area of the lateral corticospinal tract, contralateral to the lesion, contained a great number of degenerating nerve fibres. A limited amount of degeneration was also present in the same area ipsilateral to the lesion. In addition, in the ipsilateral anterior funiculus a degenerating anterior corticospinal tract was observed. Degenerating fibres and end-ramifications[1] were present in the dorsal grey matter of the spinal cord: the nucleus proprius, the basal parts of the posterior horn and the zona intermedia, contralateral to the lesion. Many of the fibres in the basal parts of the posterior horn appeared to run longitudinally. On the ipsilateral side, degenerating elements were observed in the same region, but were far less numerous. In contrast to the conditions observed in the cat, degenerating elements were also present in both anterior horns of the grey matter. In sections exhibiting a distinct spinal accessory nucleus, in the anterior horn, it appeared that only few degenerating elements distributed to this nucleus.

In sections through the decussation of the pyramidal tracts (fig. 1 B, C) massive degeneration could be traced through the decussation to the opposite lateral corticospinal tract and to a limited extent into the ipsilateral lateral corticospinal tract. Degenerating fibres could be traced also into the region at the ventral aspect and in the "hilus" of the nuclei

[1]Probably due to the survival period of thirty-six and thirty days respectively, the number of degenerating end-ramifications which could be observed was rather limited.

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cuneatus and gracilis[1] and to the spinal trigeminal nucleus and its immediate vicinity contralateral to the lesion. The substantia gelatinosa of the trigeminus on the other hand did not receive any degenerating nerve fibres. As in the dorsal grey column of the spinal cord, many of the fibres in these areas appeared to follow a longitudinal course. Moreover, the degenerating "Pick bundle" was found in this region, medial to the spinal trigeminal complex on the side contralateral to the lesion (fig. 1 C, 10). A small number of degenerating fibres was also found in the corresponding area ipsilateral to the lesion. In addition, degenerating fibres could be traced bilaterally to the nucleus supraspinalis, which forms the rostral continuation of the medial part of the anterior grey column of the spinal cord. However, only few degenerating fibres were observed in the spinal accessory nuclei. Moreover, the impression was gained that other degenerating elements passed from the decussation dorsalwards to course rostrally, ventral to the central canal and floor of the fourth ventricle respectively.

Rostral to the decussation, the spinal cord widens into the medulla oblongata. Throughout the entire extent of the medulla, degenerating fibres could be traced from the pyramidal tract in a dorsal direction. This dorsal off-set, as in the cat, was most pronounced in the more rostral parts of the medulla oblongata.

In the caudal part of the medulla oblongata (fig. 1 D–F), degenerating fibres distributed from the pyramidal tract to both halves of the brainstem, with a slight predominance of contralateral distribution. They reached the tegmental area of both sides by passing dorsalwards alongside and in part through the medial accessory olives. Here some fibres may terminate, but this number was difficult to determine because of the numerous degenerating fibres of passage.

After the fibres reached the upper part of the olivary nuclei, they fanned out into the corresponding half of the tegmentum. Some of the most medial fibres could be traced along the intramedullary roots of the hypoglossal nerves into the hypoglossal nuclei. Many degenerating elements were present in these nuclei, in largest number on the contralateral side. Since in another case, not included in this series, the difference in density of degeneration between the hypoglossal nuclei of the left and right side was much more pronounced, the impression was gained that individual differences may exist which could account for individual differences in symptomatology as described in the clinical literature. However, the number of degenerating fibres that reached the nuclei along this pathway did not seem to be great enough to explain the many degenerating elements present in these nuclei. This made it rather likely

[1]Degenerating elements were found to penetrate into the more central parts of these nuclei, but especially in the nucleus gracilis the impression was gained that the majority of the degenerating elements were confined to the spaces in between the cell clusters of this nucleus.

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that an additional pyramidal input takes place via other trajectories and most likely via the fibres which left the pyramidal tract at the decussation and passed rostralwards as described above. Some of the degenerating fibres along the hypoglossal root distributed to the paramedian reticular nuclei on both sides, which were reached also by some of the fibres ascending in the raphe.

The rest of the degenerating fibres, after reaching the dorsal margin of the inferior olive, coursed laterally and distributed diffusely over the entire tegmentum. Some such fibres could be traced bilaterally to the medial division of the lateral reticular nucleus (fig. 1 D, E) which contained a great number of degenerating elements, especially on the side contralateral to the lesion. At this level, only a very few degenerating fibres were present around the cells of the nucleus ambiguus, which obviously received far fewer degenerating fibres than, for example, the hypoglossal nuclei. Other fibres entering the tegmentum passed to the region ventral to and in the "hilus" of the nuclei cuneatus and gracilis and, in large numbers, to the spinal trigeminal nucleus and the adjacent lateral tegmental regions.[1] Especially contralateral to the lesion, this area contained a great many degenerating elements, including longitudinally oriented fibres. Here, contralateral to the lesion, the degenerating Pick bundle was found; it bent laterally and at a level half-way between the pyramidal decussation and the pons, passed over the dorsal edge of the spinal trigeminal nucleus (fig. 1 E, 10) towards the restiform body, where it could not be traced farther.

At levels involving the rostral pole of the inferior olive (fig. 1 G), the dorsal offset of degenerating pyramidal fibres became more massive. Such fibres fanned out over both halves of the tegmentum, in largest numbers to the medial part of the tegmentum ipsilateral to the lesion, and to both spinal trigeminal nuclei and the adjoining lateral parts of the tegmentum, with a dominance of the contralateral distribution. Here as well as at slightly more caudal levels a few degenerating fibres were observed in the nucleus of the solitary tract and its immediate vicinity. Moreover, some degenerating fibres were present in the ambiguus nuclei.[2]

In the region between the olives and the caudal border of the pons, the dorsal offset was still considerable and the degenerating fibres left the

[1]The spinal trigeminal nucleus is difficult to delineate from the parvicellular lateral parts of the reticular formation (lateral tegmentum) which adjoins it on the medial side. Nevertheless the present findings leave little doubt that the degenerating fibres here described actually distributed to cell groups of the spinal trigeminal complex, as well as to the adjoining parts of the lateral tegmentum.

[2]The degenerating fibres and end-ramifications observed in this part of the ambiguus nucleus were not especially numerous. This may well be due to the rather long survival period, since in the chimpanzee a lesion of the lower one-third of the pre-central motor area (area 4 (FA) and area 6 (FBA)) produces the degeneration of a good many fibres and end-ramifications in this rostral part of the nucleus.

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pyramidal tract along the entire dorsal surface (fig. 1 H). A number of the most lateral fibres passed directly to the ipsilateral facial nucleus, grouped in a somewhat separate pathway. The rest of the fibres fanned out through the entire tegmentum. Some of these fibres terminated in the medial tegmental area; others could be traced to the lateral parts of the tegmentum on both sides. A number of the last-mentioned fibres passed either to the contralateral facial nucleus, or to the spinal trigeminal nuclei and the adjacent part of the lateral tegmentum, with a predominantly contralateral distribution. The distribution of the degenerating fibres throughout the facial nuclei could be studied in more detail especially in Case 3, in which the degenerating elements were unusually well stained. Of the ipsilateral facial nucleus, the dorsal and the ventral cell group of the nucleus appeared to contain the densest network of degenerating fibres and end-ramifications; the intermediate group contained much fewer degenerating elements. In the contralateral facial nucleus approximately the same distribution prevailed. A great many degenerating elements were found in all cell groups except the intermediate cell group, which like its ipsilateral partner contained less degeneration. Moreover, comparing corresponding cell groups in the ipsi- and contralateral nuclei, the impression was gained that the difference in intensity of degeneration between the left and right dorsal cell groups was less conspicuous than that between both ventral cell groups of which the contralateral one contained much more degenerating elements than its opposite member (fig. 2).

In addition, throughout the entire brain-stem a few bundles of degenerating longitudinal fibres were observed in the medial lemniscus, in a position immediately dorsal to the degenerating pyramidal tract, representing the "pes lemnisci." At the transition between the medulla oblongata and the pons some closely packed degenerating bundles left the pyramidal tract dorsalwards and apparently contributed to these degenerating bundles in the medial lemniscus.

In the caudal part of the pons (fig. 1 K), degenerating fibres reached the tegmentum by passing through the pontine nuclei which exhibited a profuse degeneration. Their distribution pattern through the tegmentum was similar to that in the rostral part of the medulla oblongata, but the fibres were less numerous. They passed again to the medial tegmentum and could in part be traced through the tegmentum to the rostral tip of both facial nuclei as well as to the trigeminal area and its vicinity, in largest numbers contralateral to the lesion. The degenerating elements were found in the lateral tegmental zone medial to the intramedullary root of the facial nerve and in the area enclosed between this root and the vestibular complex, separated from the descending trigeminal tract by the caudal pole of the trigeminal main sensory nucleus (fig. 1 K, 6). This area corresponds to the lateral half of the parvicellular nucleus of Olszewski and Baxter (1954), which occupies the lateral parts of the tegmentum. No degeneration was observed in the abducens nuclei.

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At the middle pontine levels (fig. 1 L), again, degenerating fibres could be followed through the pontine nuclei dorsalward to terminations in the ipsilateral processus tegmentalis pontis as well as in the tegmentum proper. Some fibres were found to ascend in and alongside the raphe and distributed either to the papillioform nucleus (Olszewski and Baxter, 1954) on the ipsilateral side, or to the contralateral and ipsilateral tegmentum. In the contralateral tegmentum, however, only a few degenerating elements were found. A rather large degenerating "pes lemnisci" was present in the ipsilateral medial lemniscus. Here, but especially at caudal pontine levels (fig. 1 L) bundles of closely packed degenerating fibres could be traced from the longitudinal corticofugal tracts through the pontine grey into the medial lemniscus, where they appeared to join the degenerating longitudinal bundles of the "pes lemnisci." Degenerating elements were also present in the trigeminal region. The trigeminal motor nuclei contained such elements. However, the degeneration was far less intense than that found in the facial nucleus. Furthermore, on both sides degenerating elements were observed in an area between the trigeminal motor nucleus and the main sensory nucleus, of which the latter (fig. 1 L, 38) contained hardly any degenerating elements. This region[1] probably corresponds to the rostral part of the parvicellular nucleus of Olszewski and Baxter (1954), although it is not labelled as such in their atlas. At this level, the degenerating fibres which terminate in the trigeminal area could only be traced over a small distance through the tegmentum, prior to their termination in the trigeminal region. Neither here nor at more rostral levels could the entire pathway or the missing link with the pons be identified, due perhaps to the circumstances that the pathway followed by these fibres does not parallel to the plane or sectioning.

In the most rostral parts of the pons (fig. 1 M) the pattern of distribution was similar, but the fibres to the tegmentum proper were slightly less numerous. Although at this level the trigeminal nuclei are no longer present, a few degenerating elements could still be observed in a corresponding area, ventral and medial to the ventral margin of the brachium conjunctivum.

The findings in these transverse sections suggest that the general pattern of fibre distribution to the pons and lower brain-stem in man, as observed in this material, corresponds to that already observed in the cat (Kuypers, 1956, 1958). *However, in the human brain, direct connexions to the majority of the motor nuclei were found, which were lacking in the cat.*

Some further brain-stems were cut in the sagittal plane, in an attempt to obtain more detailed information regarding the longitudinal trajectories of the degenerating fibres, observed in the transverse sections.

[1]This region, moreover, may well be in part identical with the nucleus supratrigeminalis (Lorente de Nó, 1933; Åström, 1952).

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B. Pons, Medulla Oblongata and Upper Cervical Spinal Cord of Cases 2 *and* 4, *Sagittal Series*

The study of sagittal sections revealed in general the same distribution of degenerating fibres in the pons and medulla oblongata, which was found in the transverse sections.

First and foremost, degenerating fibres were found to distribute to the motor nuclei of the trigeminal, the facial and the hypoglossal nerves, as well as in the supraspinal nuclei and the anterior horns. These degenerating elements were most numerous in the hypoglossal and facial nuclei. The trigeminal motor nuclei as well as the supraspinal nuclei contained less degenerating elements. The difference in intensity of degeneration in different parts of the facial nuclei, as observed in transverse sections, were less striking in the sagittal material. However, sagittal sections are less suitable for studying such differences, due to the absence of bilateral symmetry in such sections.

Regarding the pathway followed by the fibres distributing to these motor nuclei, the following additional information was gained. Some of the fibres which passed to the trigeminal motor nuclei to some extent followed a rostro-caudal direction, which may in part explain the difficulties encountered in tracing these fibres in the transverse series. The degenerating fibres to the facial nuclei seem to approach these nuclei predominantly from the medial side; hardly any longitudinally coursing degenerating fibres appeared to enter these nuclei. On the other hand, the degenerating fibres entering the hypoglossal nuclei approached them from the ventral as well as from the caudal side. The fibres approaching from the ventral side coursed parallel to the intramedullary rootlets of the hypoglossal nerves, whereas the other fibre group separated itself from the pyramidal tract in the decussation and passed rostrally as recurrent pyramidal fibres (fig. 3 B–D).

Degenerating elements were observed throughout the entire caudo-rostral extent of the spinal trigeminal complex, as well as in the adjacent lateral tegmentum continuing rostrally up to the level of the isthmus. Although present on both sides, the degeneration was less massive in the caudal parts of the ipsilateral trigeminal area than in the corresponding region of the contralateral side. Moreover, in this region a number of degenerating fibres exhibited a longitudinal course (fig. 3 F) whereas others coursed ventro-dorsally and seemed to enter the area from the ventral side. In the transverse sections it was found that only very few degenerating fibres distribute to the territory of the trigeminal main sensory nucleus, while a great many passed to the area adjoining it on the medial side. This was also noticeable in the sagittal sections, where, moreover, the impression was gained that these few fibres were located mainly in between the cell clusters of this nucleus.

The degenerating fibres at the ventral aspect and in the "hilus" of the

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nuclei cuneatus and gracilis were also in evidence in the sagittal sections. The majority of these elements exhibited a longitudinal course and, as those to the hypoglossal nuclei, were apparently recurrent pyramidal fibres separated from the pyramidal tract at the decussation to course rostralwards through this area (fig. 3 C–E).

The dorsal pyramidal off-set observed in the transverse sections could also be identified in the sagittal series. Throughout the entire medulla oblongata, from the pyramidal decussation up to the pons, degenerating fibres could be traced from the pyramidal tract in the dorsal direction. Such fibres were most numerous in the rostral parts of the medulla oblongata. Moreover, as in frontal sections, the fibres in the caudal parts of the medulla were found to course through the medial accessory olives. Throughout the entire medulla as well as in the most caudal parts of the pons, these fibres could be traced to the more dorsal parts of the tegmentum including the paramedian reticular nuclei. A great many degenerating fibres and end-ramifications were present scattered throughout this area. Differences in intensity of degeneration between the ipsilateral and contralateral halves of the tegmentum were less obvious in the sagittal sections.

In the medial lemniscus a number of compact degenerating longitudinal bundles were found, which parallel the degenerating pyramidal tract, and corresponded to similar findings in the frontal sections. These closely packed degenerating bundles, undoubtedly representing the "pes lemnisci," could be traced throughout the region extending from the rostral parts of the pons to the level of the pyramidal decussation (fig. 3 B, 44). These bundles, which separate from the corticofugal tracts in the mesencephalon, coursed over the dorsal aspect of the pontine grey, separated by a considerable distance from the corticofugal tracts, which are embedded in the pontine nuclei. In the caudal parts of the pons, these two corticofugal components drew nearer to each other, due to the decrease in volume of the pontine nuclear mass. At transitional levels between the pons and medulla oblongata, an exchange of fibres seemed to take place between both systems. Some degenerating bundles could be traced from the pes lemnisci into the pyramidal tract, while others appeared to pass from the pyramidal tract to the pes lemnisci. However, other bundles of the pes lemnisci continued their course in the medial lemniscus to join the pyramidal tract at more caudal levels of the medulla oblongata. The impression was gained that at least a number of fibres from these bundles distributed to the mid-line nuclei in the pons and the tegmentum of the medulla oblongata.

Pick's bundle, which constitutes a further aberrant pyramidal system identifiable in frontal sections, was again observed in the sagittal series (fig. 3 F, 10) medial to the spinal trigeminal nucleus. The sagittal sections, however, proved less suitable for studying in detail the lateral curvature of this bundle.

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As in the medulla oblongata, degenerating elements were also found in the pontine tegmentum, in largest numbers ipsilateral to the lesion.

C. Caudal Part of the Medulla Oblongata of Case 3, Cut in Longitudinal Sections Forming an Angle of 50 Degrees with the Sagittal Plane

The distribution of degenerating fibres found in this series was similar to that observed in sagittal and frontal sections. The special orientation of the sections, however, made it possible to study the recurrent pyramidal fibres in more detail. Unlike the other series, sections oriented in this manner permit a survey of the entire length of the pyramidal tract, including its decussation in single sections. The study of such sections revealed that a fair number of degenerating fibres left the pyramidal tract at the level of the decussation, to course rostralwards as recurrent fibres through the region at the ventral aspect and in the "hilus" of the nuclei cuneatus and gracilis and in the medial part of the spinal trigeminal nucleus and the adjacent part of the tegmentum. Such "ascending" fibres represented, in a sense, a mirror image of the "descending" lateral corticospinal tract entering its spinal trajectory. In addition, in these sections degenerating fibres could be traced from the degenerating pyramidal tract across the mid-line into the opposite tegmentum. Some of these fibres represent an additional distribution of the pyramidal tract to the spinal trigeminal complex and the lateral tegmentum.

KEY TO THE NUMBERING OF TEXT FIGURES

1. Lateral corticospinal tract.
2. Anterior corticospinal tract.
3. Anterior horn.
4. Decussation of the pyramidal tracts.
5. Supraspinal nucleus.
6. Trigeminal complex and the adjacent lateral tegmentum.
7. Nucleus cuneatus.
8. Nucleus gracilis.
9. "Pyramidal tract."
10. Pick's bundle.
11. Ambiguus nucleus.
12. Inferior olive.
13. Lateral reticular nucleus.
14. External cuneate nucleus.
15. Hypoglossal nucleus.
16. Intramedullary root of the hypoglossal nerve.
17. Dorsal motor nucleus of the vagus nerve.
18. Solitary tract and its nucleus.
19. Restiform body.
20. Vestibular complex.
21. Posterior funiculus.
22. Root of the vagus nerve.
23. Cochlear nuclei.
24. Glossopharyngeus nerve.
25. Nucleus præpositus.
26. Nuclei of the posterior funiculus.
27. Facial nucleus.
28. Brachium pontis.
29. Root of the facial nerve.
30. Vestibular nerve.
31. Abducens nucleus and abducens nerve.
32. Raphe.
33. Pontine nuclei.
34. Superior olive.
35. Brachium conjunctivum.
36. Root of the trigeminal nerve.
37. Trigeminal motor nucleus.
38. Trigeminal main sensory nucleus.
39. Medical lemniscus.
40. Lateral lemniscus.
41. Processus supralemniscalis pontis.
42. Mesencephalic root of the trigeminal nerve.
43. Nucleus cæruleus.
44. Pes lemnisci.
45. Nucleus papillioformis.
46. Nucleus of the lateral lemniscus.

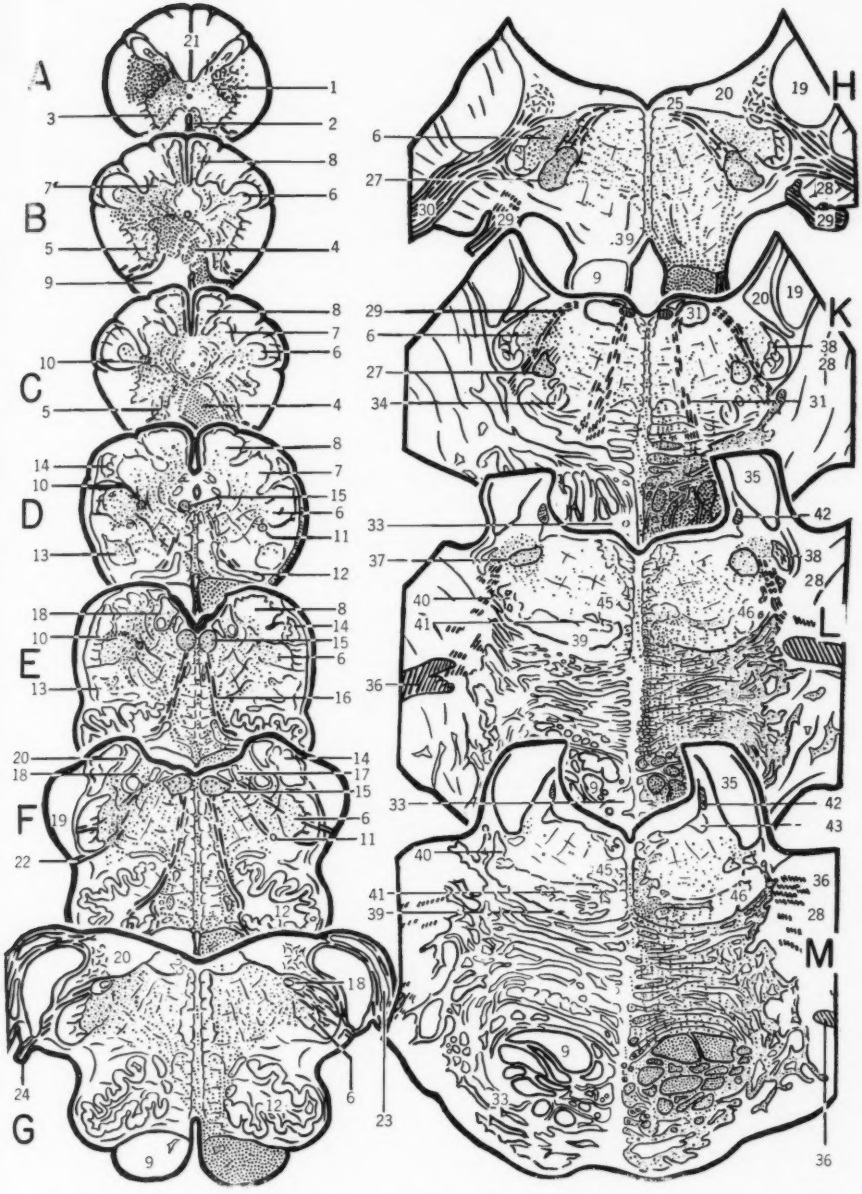

FIG. 1.—Semi-diagrammatic representation of the distribution of degenerating elements in the pons and lower brain-stem of Case 1, transverse sections. Coarse stippling indicates degenerating axons, fine stippling indicates degenerating, end-ramifications. Numbering, *see* page 374.

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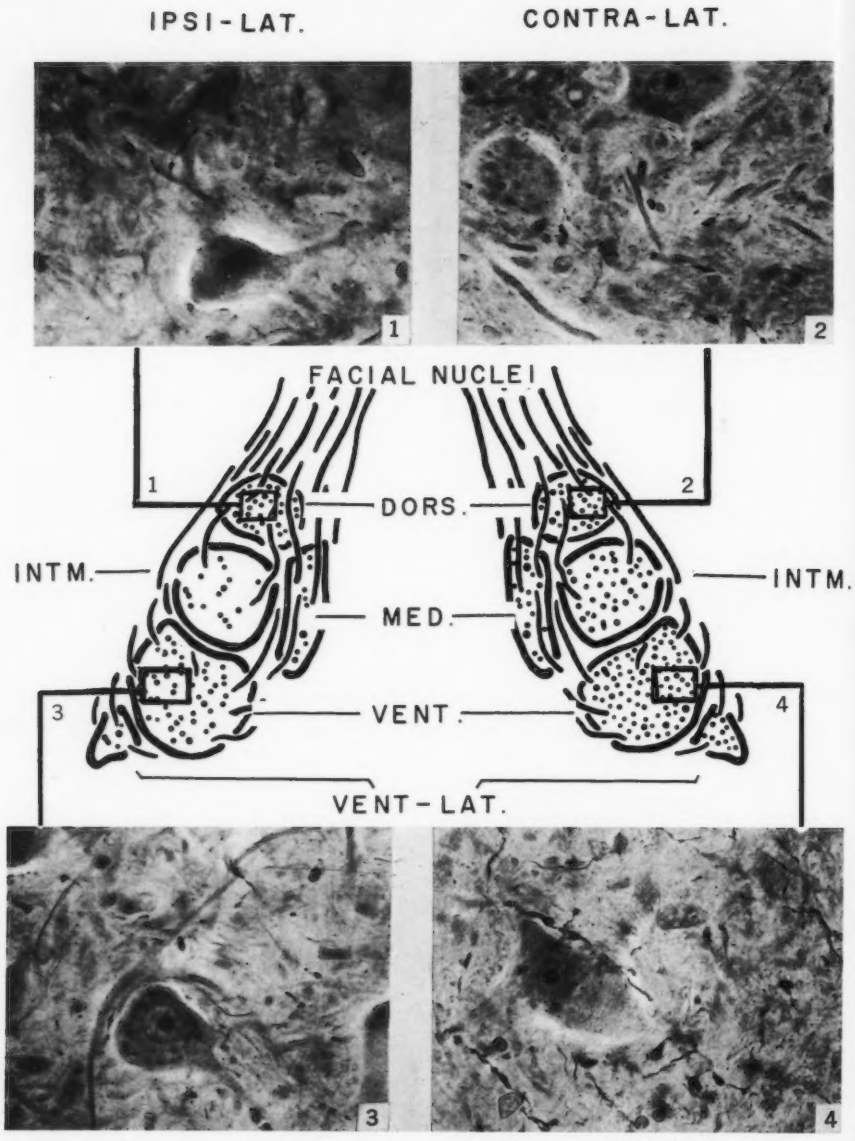

FIG. 2.—Diagrammatic approximation of the distribution of degenerating fibres and end-ramifications to the main cell groups of the facial nuclei, as observed in Case III. Photographs, 1: ipsilateral dorsal nucleus; 2: contralateral dorsal nucleus; 3: ipsilateral ventral nucleus; 4: contralateral ventral nucleus. Note the quantitative difference between 3 and 4. Nauta–Gygax. ×500.

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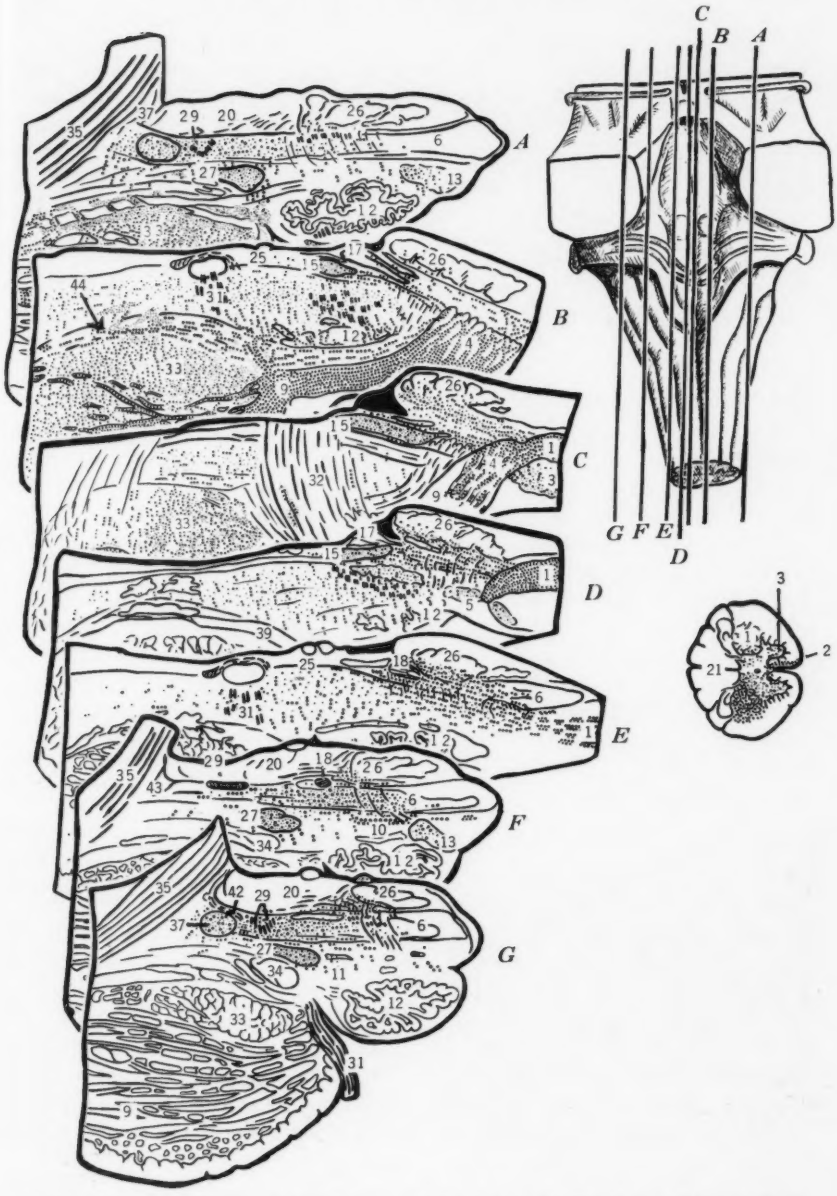

FIG. 3.—Semi-diagrammatic representation of the distribution of degenerating fibres in the pons and lower brain-stem of Case IV, sagittal sections. Symbols used as in fig. 1. Numbering, *see* page 374.

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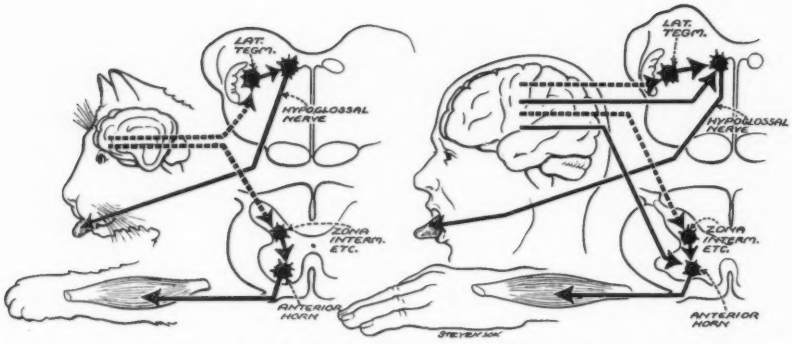

FIG. 4.—Diagram illustrating the differences in corticofugal connexions in cat and man.

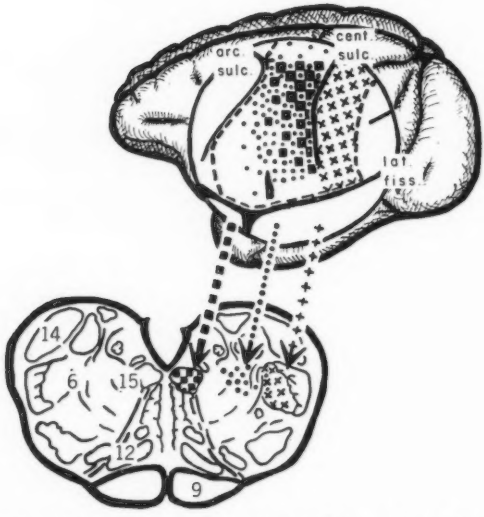

FIG. 5.—Diagrammatic summary of the differential origin in the monkey of the peri-central projections to the motor nuclei, the spinal trigeminal complex and the adjacent lateral tegmentum (Kuypers, *J. Comp. Neur.*, in the press).

IV. Discussion

The observations described in the foregoing chapters can be summarized as follows. Following lesions of the hemisphere, including parts of the basal ganglia, in the human brain, degeneration was observed in the following areas of the pons and the medulla oblongata:

(1) A region ventral to and in the "hilus" of the nuclei cuneatus and gracilis, extending into the spinal trigeminal nucleus and the lateral part of the tegmentum adjacent to this nucleus and continuing rostrally to the level of the isthmus;

(2) the central regions of the tegmentum of the medulla oblongata;

(3) the medial part of the lateral reticular nucleus of the medulla, mostly contralateral to the lesion;

(4) the tegmentum of the pons, predominantly as in the pontine nuclei ipsilateral to the lesion.

The region ventral to and in the "hilus" of the nuclei cuneatus and gracilis, as well as in the trigeminal complex and its vicinity is supplied by both transtegmental and recurrent pyramidal fibres. In addition, the aberrant pyramidal system represented by the "pes lemnisci" was found to degenerate and the impression was gained that this system distributes part of its fibres to the tegmentum of the pons and the medulla oblongata. Furthermore, in 2 of the 4 cases studied a degenerating "Pick bundle" was observed contralateral to the lesion.

It must be emphasized that a great many degenerating fibres were consistently observed to terminate in the motor trigeminal, facial, hypoglossal and supraspinal nuclei. The spinal accessory nuclei contained only a few degenerating elements, and none were present in the abducens nuclei. Terminal degeneration in the ipsilateral facial nucleus, although present throughout the nucleus, was most concentrated in the dorsal and ventral cell group.

With the exception of the degeneration in the cranial motor nuclei, the distribution of corticofugal fibres to the brain-stem as here described in human material is in general similar to that in the cat (Kuypers, 1956, 1958) following ablation of sensorimotor cortex, either singly or combined with destruction of the basal ganglia. In the experiments in the cat, however, very few if any degenerating fibres or end-ramifications were present in the cranial motor nuclei. This seems to suggest that one of the essential anatomical differences in efferent projection between the human[1] and the cat's cortex respectively consists in the presence in man of an additional system of direct projections to the cranial motor nuclei.

Before going into a detailed discussion of these differences, the observations described above will be confronted with the anatomical data available

[1]On the basis of the present study the basal ganglia cannot be ruled out as an additional source of these projections. However, such connexions seem rather unlikely.

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in the literature, with special emphasis on the studies of human material. A perusal of the literature revealed that direct cortical projections to the motor nuclei were observed earlier by Weidenhammer (1896), Hoche (1898), Barnes (1901) and Sand (1903), with the aid of the Marchi technique in human pathological material, in which lesions were present involving either the cortex alone or the cortex together with deeper structures of the hemisphere.

The bilateral connexions with the trigeminal motor nuclei were mentioned by the majority of these authors. Hoche (1898) stated in addition that such fibres were limited in number and could be traced over only a short distance from the nuclei. They also found fibre connexions with both facial nuclei, but the distribution of these fibres throughout the ipsilateral facial nucleus as studied in the present material was never described. Degenerating fibres to both hypoglossal nuclei were also reported, reaching these nuclei along the intramedullary part of the hypoglossal nerve. As mentioned above, it became obvious in our material that this is not the only pathway to these nuclei, since recurrent pyramidal fibres could be identified as an additional afferent system. Such a pathway was never described in human material, but was reported by Glees (1956b) in the monkey.

The authors paid little attention to the cortical projections to the spinal accessory nuclei. However, Hoche (1898) stated that hardly any fibres could be traced to these nuclei in his material, a statement which agrees well with our observations.

In addition to the corticonuclear fibres, the authors also observed the degeneration of the pes lemnisci. This system, described in detail by Dejerine (1901) probably represents an aberrant pyramidal system; which according to Verhaart (1935) became separated during phylogenesis from the bulk of the corticofugal tracts by the increasing development of the dorsal pontine nuclei. Following Dejerine (1901) at least part of these bundles join the pyramidal tract rostral to the pyramidal decussation, as could be confirmed in our material. Hoche (1898) as well as Barnes (1901) were of the opinion that the aberrant pyramidal bundles of the pes lemnisci as well as the pyramidal tract itself distribute fibres to the motor nuclei. Sand (1903), on the other hand, expressed the view that such fibres are derived only from the "pyramidal tract" proper. In our material this was difficult to determine, but the impression was gained that the pes lemnisci distributes fibres to the tegmentum. However, the observations of Krieg (1954) in monkey material, render it unlikely that the pes lemnisci is an important carrier of corticonuclear fibres, since this system according to Krieg (1954) seems to originate in a cortical area in front of the motor cortex proper. The studies of Verhaart (1935), on the other hand, indicated that the origin of some of these fibres in the monkey is located in the precentral gyrus.

Furthermore, in human material, Barnes (1901) and others observed

the degeneration of the recurrent pyramidal bundle of Pick (1890). As in Pick's original material, in the present material this bundle could be traced cranially into the medulla oblongata, where it passsed in the direction of the restiform body. Barnes (1901) assumed that this bundle formed the corticobulbar pathway to the ambiguus nucleus. Weidenhammer (1896), on the other hand, expressed the view that such fibres were instead represented by the pyramidal fibres which pass to the lateral part of the tegmentum of the lower medulla oblongata. As shown above, the majority of these fibres pass to other destinations in the lateral tegmentum, although a few such elements may indeed terminate in the region of the ambiguus nucleus.

The connexions with the region at the ventral aspect and in the "hilus" of the nuclei cuneatus and gracilis and with the spinal trigeminal nucleus and the lateral part of the tegmentum appear not to have been described previously in human material, with the exception of the publication of Weidenhammer (1896) who observed some fibres passing to the lateral part of the tegmentum. In studies dealing with animal material these connexions were observed. Regarding the connexions with the region of the nuclei cuneatus and gracilis, Redlich (1897) already traced with the Marchi technique a few degenerating fibres from the pyramidal tract to these nuclei in the cat. Nisino (1940) indicated (his fig. 14A) the presence in the monkey of a few degenerating fibres in this region as well as in the lateral tegmentum and the spinal trigeminal nucleus, after extensive cortical damage. Most recently Walberg (1957) reported degenerating terminals in especially the ventral parts of these nuclei in the cat, following extensive cortical damage. This location, in all likelihood, is similar to what is called in the present study the region at the ventral aspect and in the "hilus" of the nuclei cuneatus and gracilis. Moreover, Mettler (1935) reported degenerating fibres passing to the spinal trigeminal nucleus in the monkey after lesions of the motor cortex; most recently Torvik (1956) described such fibres in the rat while Brodal *et al.* (1956)[1] as well as the present author (1956) found them in the cat. On the other hand, the existence of a considerable number of recurrent pyramidal fibres paralleling Pick's bundle and supplying these regions appears to have been overlooked by previous workers. In respect to such recurrent pyramidal fibres, the impression was gained that they represent the expression of a general distribution pattern of the pyramidal fibres, especially since they course through an area which is approximately homologous to the area

[1]Most recently Brodal, Szabo and Torvik (*Journal of Comparative Neurology*, 1956, 106 add. Vol., 527–555) reported about the presence of the degenerating fibres in the spinal trigeminal nucleus of the cat after cortical lesions. However, after such lesions they also observed heavy degeneration in the main sensory nucleus and the substantia gelatinosa of the trigeminus, which we were unable to detect in either cat or human material.

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of the lateral corticospinal tract in the spinal cord. Pick's bundle conforms to the same pattern.

The fibre connexions with the tegmentum of the pons and the medulla oblongata were also observed in the human material studied by Hoche (1898) and Sand (1903). For a further review of the data regarding such connexions, reference is made to Rossi and Brodal (1956). We want, however, to emphasize again the dominance of the ipsilateral fibre distribution to the pontine tegmentum in the cat and man. The observation made by McCulloch *et al.* (1946), indicated the presence of a corticofugal projection from area "4S" to the tegmentum of the medulla, passing through the pons separated from the bulk of the corticofugal fibres. Such a projection corresponds in all likelihood to those fibres of the pes lemnisci which distribute to the tegmentum as observed in our material.

The projections to the lateral reticular nuclei, were described by us in detail in the cat (Kuypers, 1958) and were also indicated by Rossi and Brodal (1956).

It appears appropriate next to discuss the functional aspects of the connexions here considered since it is logical to assume that they must form the substratum of a number of clinical phenomena. First and foremost, the anatomical finding of a bilateral fibre distribution to the trigeminal motor and hypoglossal nuclei could, as suggested previously by others, account for the transitory nature of the supranuclear paralysis of the jaw and tongue musculature which follows unilateral lesion of the internal capsule. Moreover, as indicated by the present findings, individual differences seem to exist in regard to the volume of corticofugal connexions with the ipsilateral hypoglossal nucleus. Although the mechanism of cortical control over the tongue movements is probably rather complex, such observations may nevertheless explain individual differences in symptomatology, e.g. some exceptional cases of permanent paralysis of the tongue following internal capsule hæmorrhage (Foerster, 1936).

Such clinical and anatomical observations receive additional support from physiological findings. Penfield and Rasmussen (1950), for example, could frequently elicit bilateral movements of the jaw and tongue by stimulation of the human motor cortex. The same holds true for the movements of the eyebrows and eyelids, which brings us to a discussion of the bilateral fibre distribution to the facial nucleus.

It is a general experience that the supranuclear paralysis observed in clinical neurology is most prominent around the mouth, while the frontal facial movements on the other hand, although sometimes slightly affected, recover rather quickly. Since the end of the last century, a great many clinical neurologists have assumed that the cells in the facial nucleus which innervate the upper facial musculature receive cortical motor fibres from both hemispheres. However, some authors have expressed the view that these muscles may be innervated through the facial nerve by cells

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located outside the facial nucleus, e.g. in the eye muscle nuclei. Another explanation for the phenomenon could be found in the observation that some fibres from the intramedullary root of the facial nerve seem to cross over to join the contralateral facial nerve, as described among others by Cajal (1909) and more recently by Pearson (1947). However, the lack of retrograde changes in the contralateral facial nucleus after section of the facial nerve, as pointed out by Papez (1927) and others makes this subject rather controversial. Consequently, we will limit the discussion to the bilateral corticofugal fibre distribution to the facial nucleus. In our material the degenerating fibres to the ipsilateral nucleus, already reported by Weidenhammer (1896), Hoche (1898), Barnes (1901) and Sand (1903), distributed throughout the nucleus, but were most numerous in the dorsal and the ventral cell group. The traditional clinical assumption that the cells innervating the superior facial musculature receive a bilateral cortical projection could thus be substantiated further, if it could be demonstrated that indeed cells of the dorsal or the ventral cell group or both, are related to the superior facial musculature. The problem of topical organization in the facial nucleus, was studied experimentally in animals among others by Van Gehuchten (1898), Marinesco (1899), Yagita (1910), Papez (1927), and most recently by Vraa-Jensen (1942). Generally speaking, the results of these investigations seem to be in good mutual agreement, although differences in classification and nomenclature of the facial cell groups sometimes render the comparison of individual results somewhat less than reliable. According to Papez, the frontal and circum-ocular muscles in the dog are innervated by the cells of the dorsal group, whereas the cells of the ventral and ventrolateral group innervate muscles around the mouth, and those of the medial group, the musculus platysma. However, Szentagothai (1948), who studied the functional topography of the facial nucleus by stimulation and destruction of different parts of the nucleus in the dog, came to the conflicting conclusion that frontal and circum-ocular muscles are innervated by cells in the lateral part of the nucleus.

Van Buskirk (1945) pointed out, followed by Pearson (1946), that in man the axis of the nucleus, as appearing in frontal section, is oriented from dorsomedial to ventrolateral, whereas in the dog the axis of the nucleus is oriented more horizontally. He suggested that the functional organization of the human nucleus could be inferred from Papez's (1927) experimental findings in the dog, if only this rotation were taken into account. This concept would suggest that the medial cell group of the dog is identical with the dorsal cell group of man, whereas the dorsal cell group of the dog would correspond to the intermediate cell group of man. However, if this were the case, the findings in our material would have demonstrated that the cells innervating the frontal muscles located in the intermediate cell group, receive a minor number of ipsilateral corticofugal fibres, in contrast to cells related to other parts of the facial muscula-

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ture; a conclusion obviously in conflict with the classical hypothesis. On the other hand, it must be pointed out that the study of the facial nucleus in man in cases of neoplastic destruction of different branches of the nerve and the corresponding muscles suggests a different organization.

Parhon and Minea (1907) reported conspicuous retrograde cell changes in the facial nucleus, almost entirely limited to the dorsal cell group, in cases of destruction of the superior facial musculature and the corresponding branches of the facial nerve in man. This observation is in perfect agreement with Hudovernig's (1908) findings in a similar case, and together with the data obtained from our own material would appear to substantiate the traditional clinical supposition that the cells innervating the upper facial musculature receive a cortical projection from both hemispheres. According to Parhon and Papinian (1904) and Hudovernig (1908), the ventral cell group innervates the lower facial musculature. If this is correct, the bilateral corticofugal connexions with this cell group could be responsible for voluntary bilateral lip movements which may be left intact in the presence of hemiplegia. *However, although this cell group receives a substantial bilateral cortical projection, the terminal degeneration in the ventral cell groups of the contralateral nucleus was considerably more intense than in the same cell group of the ipsilateral nucleus, whereas such left-right differences were less pronounced in the dorsal cell groups.* This could indeed help to explain the functional differences between both groups of facial musculature in cases of hemiplegia; but it must be kept in mind that the possibility of an intramedullary decussation of root fibres has not been ruled out entirely, a circumstance which complicates the issue even further.

The functional aspects of the cortical projection to the trigeminal complex and the adjacent lateral tegmentum, as well as to the region of the nuclei cuneatus and gracilis are much more difficult to discuss. However, the results of our experimental studies of these connexions in the cat (Kuypers, 1958) and in the monkey and chimpanzee (Kuypers, in the press) may contribute to the understanding.

It was found that, as far as the cat's motor cortex is concerned (Kuypers, 1958), the face area constitutes the main origin of the fibres to the trigeminal complex and the lateral tegmentum. Since in this animal cortical connexions to the motor nuclei are almost completely absent, it could be suspected that these cortical fibres constitute the corticofugal link in an "indirect" corticonuclear pathway interrupted by one or more synapses in the trigeminal and/or juxta-trigeminal cell groups. This suggestion would be consistent with Cajal (1909) and Lorente de Nó's (1933) description of projections from the trigeminal nucleus and adjacent cell groups to the motor nuclei, as well as with the observations that in the cat lesions in this area produce profuse terminal degeneration in the motor nuclei (Nauta and Kuypers, in the press). Such an arrangement would be similar

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to that already known in the spinal cord of this animal, where the corticofugal impulses are almost exclusively relayed to the anterior horn cells by way of internuncial elements (Szentagothai, 1941; Lloyd, 1941; Chambers and Liu, 1957).

It is of great interest to note that in the present study in man a similar distribution of degenerating fibres to the trigeminal complex and the adjacent lateral tegmentum was found. Here, however, these presumably "indirect" corticonuclear connexions appear to be augmented by a massive system of direct corticonuclear projections, virtually lacking in the cat (fig. 4). These anatomical findings seem to parallel Bernhard and Bohm's (1954) electrophysiological observations which indicate the existence in the monkey of a set of "direct" as well as "indirect" projections from the arm and leg area of the pre-central motor area to the motor neurons in the spinal cord; while in the cat only the "indirect" connexions could be demonstrated.

Further anatomical experiments (*J. Comp. Neur.*, in the press) have demonstrated that these fibre systems projecting to the motor nuclei, the trigeminal complex and the adjacent lateral tegmentum are also present in the monkey, and in addition possess a differential cortical origin. It was found in this animal that *the corticofugal fibres to the trigeminal complex constitutes primarily a post-central projection, whereas the cortical fibres to the lateral tegmentum and the motor nuclei arise almost exclusively from the pre-central territories.* Moreover, regarding this pre-central outflow it could be demonstrated that the direct corticonuclear connexions originate predominantly in the caudal parts of the lower one-third of the pre-central gyrus, whereas the field of origin of the projections to the lateral tegmentum extends more rostrally, both having the central sulcus as a common caudal border (fig. 5). These observations suggest that the post-central cortical fibres to the trigeminal complex, which arise from the somato-sensory cortex proper, subserve primarily a "sensory" function, by influencing the threshold of primary sensory synapses (Hagbarth and Kerr, 1954). The pre-central projections to the motor nuclei and the lateral tegmentum on the other hand, are likely to subserve more truly "motor" functions. Consequently, it would indicate that the internuncial elements are more specifically located in the lateral tegmentum rather than in the trigeminal complex. This is consistent with the observation that the lateral tegmentum constitutes the uninterrupted rostral continuation of the zona intermedia and the basal parts of the posterior horn in the spinal cord, which contain the majority of the spinal internuncial elements (Lloyd, 1941).

Regarding the corticofugal connexions to the region of the nuclei cuneatus and gracilis, it was found (Kuypers, 1958) that as far as the cat's motor cortex is concerned these projections originate predominantly in the hind- and fore-limb areas respectively. The same holds true for

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the monkey, where in addition a great many such fibres also appeared to originate from the post-central gyrus. If the present line of thinking is correct, these projections constitute another descending sensory "feed-back" system, similar to that from the post-central gyrus to the trigeminal complex, which in the same fashion may influence the threshold of the primary sensory synapses in the nuclei of the posterior funiculus. A more detailed report on these and similar projections will be published separately at a later date.

Summary

The distribution of degenerating fibres was studied in the medulla oblongata and the pons of four human brains, in which either an encephalomalacia was present, due to occlusion of the middle cerebral artery, or a hæmorrhage in the internal capsule. This was done with the aid of the Nauta–Gygax silver impregnation technique.

In these brain-stems, many degenerating fibres were distributed to the trigeminal motor, facial, hypoglossal and supraspinal nuclei, whereas the spinal accessory nuclei received only a few degenerating fibres and none were present in the abducens nuclei. In view of its clinical importance, the distribution of degenerating elements throughout the ipsilateral facial nucleus was studied in more detail.

Moreover, the accumulation of degenerating fibres and end-ramifications present in the dorsal grey substance of the spinal cord, was found to continue rostralwards throughout the entire lower brain-stem. Degenerating elements were observed in the region ventral to and in the "hilus" of the nuclei cuneatus and gracilis, as well as in the spinal trigeminal complex and the lateral tegmentum up to the level of the isthmus. In addition, degenerating fibres were found to be distributed to the ipsilateral pontine tegmentum, the medial part of the tegmentum of the medulla oblongata as well as to the lateral reticular nucleus of the medulla, predominantly contralateral to the lesion.

A similar distribution of degenerating elements was found earlier (Kuypers, 1956, 1958) in the cat, after either lesions of the motor cortex or hemispherectomy. However, in this animal, the degenerating fibres to the motor nuclei were almost completely lacking. In view of these and more recent findings in the monkey, it would appear that specifically the fibres to the lateral tegmentum represent the corticofugal link in a phylogenetically older indirect corticonuclear pathway interrupted by one or more synapses in this region, and which in man is paralleled by a more recent direct corticonuclear system.

Acknowledgment

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LEGENDS TO PLATES

PLATE LIII

ILLUS. 1.—Degenerating elements in the region at the ventral aspect of the nucleus cuneatus. Transverse section. Nauta and Gygax. ×250.

ILLUS. 2.—Degenerating nerve fibres and end-ramifications around a cell of the hypoglossal nucleus. Sagittal section. Nauta and Gygax. ×500.

ILLUS. 3.—Degenerating nerve fibres and end-ramifications surrounding cells of the hypoglossal nucleus. Sagittal sections. Nauta and Gygax. ×500.

ILLUS. 4.—Degenerating nerve fibres in the tegmentum of the medulla oblongata. Sagittal section. Nauta and Gygax. ×400.

ILLUS. 5.—Some degenerating longitudinal fibres in the region at the ventral aspect of the nucleus cuneatus. Sagittal section. Nauta and Gygax. ×400.

ILLUS. 6.—Degenerating elements in the medial part of the spinal trigeminal nucleus and the adjacent part of the tegmentum. Sagittal section. Nauta and Gygax. ×400.

PLATE LIV

ILLUS. 7.—Degenerating nerve fibres in the ipsilateral pontine nuclei. Nauta and Gygax. ×±500.

ILLUS. 8.—Contralateral pontine nuclei. Note the absence of degenerating nerve fibres. Nauta and Gygax. ×±500.

ILLUS. 9.—Degenerating nerve fibres in the ipsilateral pyramidal tract (sagittal section). Nauta and Gygax. ×±500.

ILLUS. 10.—Contralateral pyramidal tract. Note the absence of degenerating nerve fibres (sagittal section). Nauta and Gygax. ×±500.

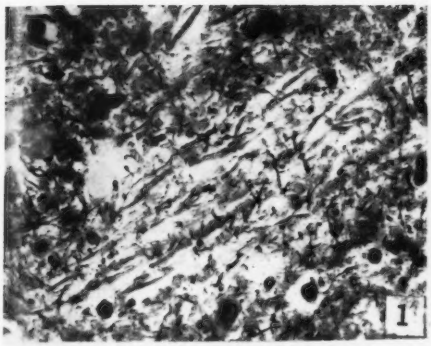
ILLUS. 11.—Nerve cells of the abducens nucleus. Note the absence of degenerating nerve fibres and end-ramifications. Nauta and Gygax. ×±500.

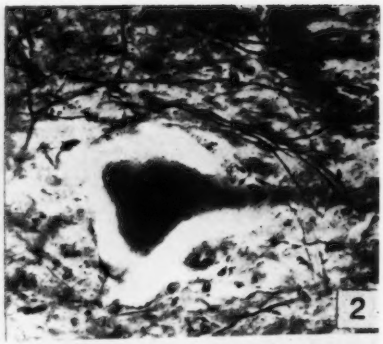
ILLUS. 12.—Degenerating nerve fibres in the lateral tegmentum of the medulla oblongata. Nauta and Gygax. ×±500.

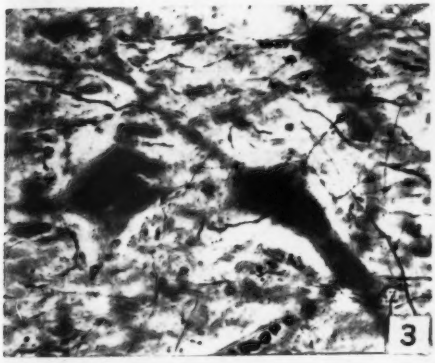
ILLUS. 13 and 15.—Degenerating nerve fibres and end-ramifications around cells of the trigeminal motor nucleus. Nauta and Gygax. ×±500.

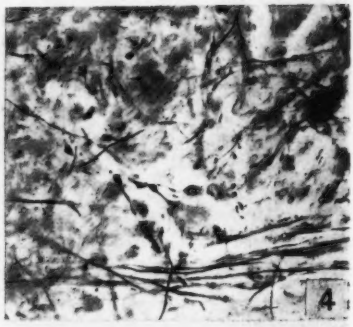
ILLUS. 14.—Cell cluster of the main sensory nucleus of the trigeminus (nucleus principalis trigemini). Note the absence of degenerating nerve fibres and end-ramifications. Nauta and Gygax. ×±500.

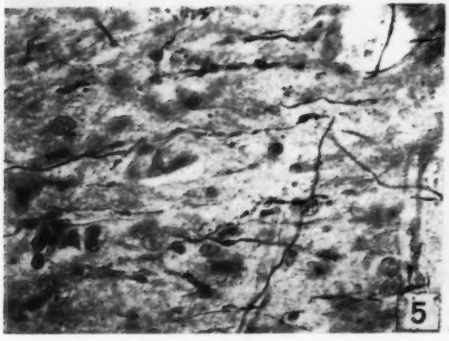
PLATE LIII











To illustrate article by H. G. J. M. Kuypers.

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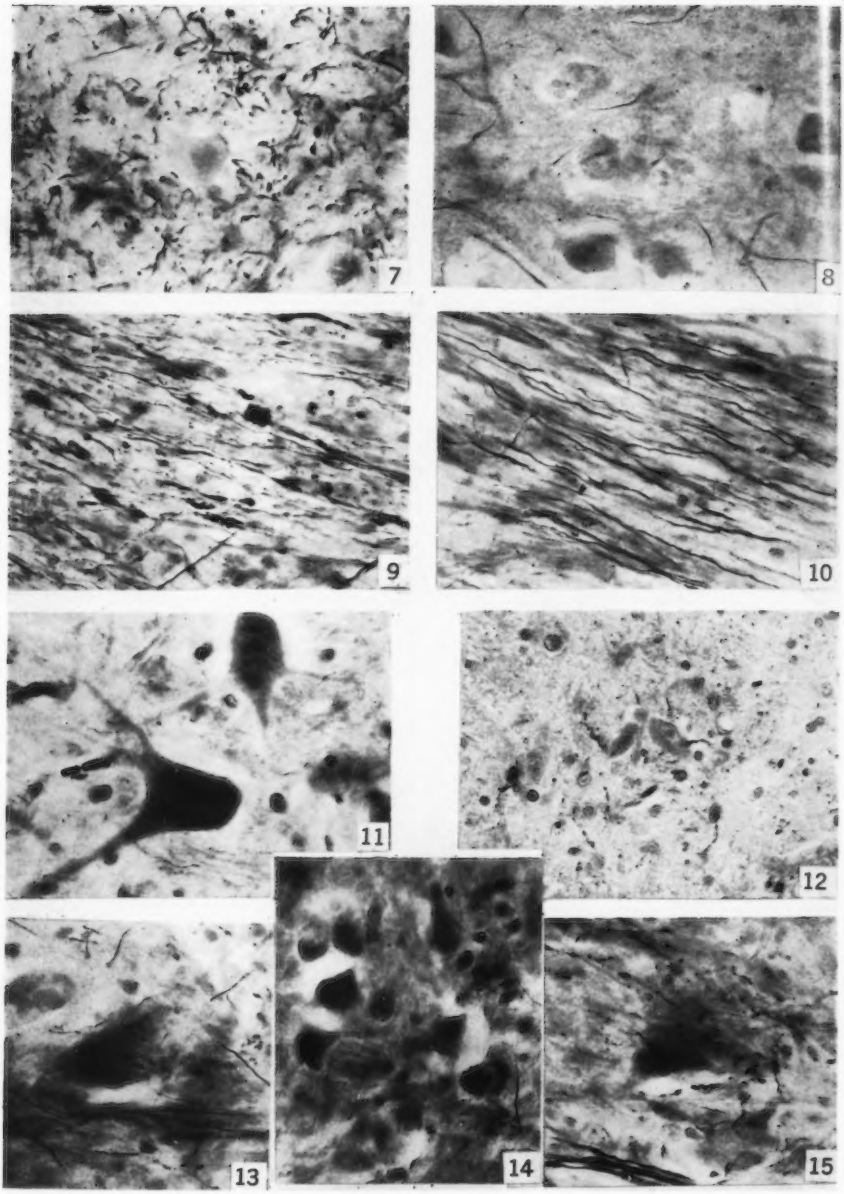
PLATE LIV



To illustrate article by H. G. J. M. Kuypers.

ON CERTAIN SMALL TUMOURS ENCOUNTERED IN THE TEMPORAL LOBE

BY

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INTRODUCTION

IT may in general be presumed that epileptic seizures of focal character in a susceptible subject are a most sensitive indicator of local brain damage, provided that cortical or subcortical white matter is involved by the process. In retrospect, therefore, it should not have been a matter for surprise that careful study of epileptogenic areas removed from such subjects would reveal occasional pathological changes at an earlier state of development than usually encountered in post-mortem material. When, however, it transpires that these changes are small tumour-like formations with indications in some areas of early neoplastic transformation; that their nature was entirely unsuspected in several instances before operation, despite clinical histories for the most part of more than ten years' duration and long periods of medical supervision; and that the incidence of these formations in a group of patients selected for their epileptic problems is 10–12 per cent, it is plain that such findings must claim some interest. In the clinical and diagnostic fields this conclusion will be undoubted. To those concerned with the natural history of gliomas these observations should at once raise questions of a fundamental nature not readily posed by traditional post-mortem approach which only too frequently sees the beginnings of pathological processes blurred and distorted by the accumulation of secondary changes.

The temporal lobe material of the Guy's-Maudsley Neurosurgical Unit is unique, not only because of the wealth of clinical detail gathered, although in numbers it is considerably less than that of the Montreal School (Earle, Baldwin and Penfield, 1953), but particularly in the manner of its subsequent investigation. It is due to this painstaking study that several of the smaller and possibly for that reason more important changes in this series have come to light. In this report eight examples of small tumorous lesions of the temporal lobe are described

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from patients suffering from psychomotor epilepsy, for the most part of long duration and often accompanied by disorders of character and behaviour. The report is chiefly a pathological one and for that reason the short clinical histories include only such material that may be considered as throwing light upon the natural history of the lesions. A more detailed clinical report in which particular regard will be paid to the epileptic manifestations of these subjects will be published elsewhere.

Material and Methods

All cases were of proven intractability to anti-convulsant drugs, and all were subjected to a full clinical investigation which included multiple electro-encephalographic recordings, X-ray air studies and psychometric testing, upon the combined results of which the decision as to the side to be operated upon was taken. Unilateral extirpation of the anterior two-thirds of the temporal lobe was done in all cases. Particular efforts were made during operation to include Ammon's horn, the uncus and the basal parts at least of the amygdaloid complex in the specimen. The lobe was fixed in formal-saline and sliced coronally into blocks from 0·5–1·0 cm. thick. These were embedded in celloidin and groups of sections 20–30 μ thick were stained with cresyl violet, Mallory, van Gieson and myelin stains after every 50th section cut (i.e. at approximately 1 mm. levels in the dehydrated specimen). Where lesions were recognizable in the gross specimen a few frozen sections were taken for the silver and fat staining methods before embedding. The absence of the silver techniques for displaying finer cytological detail was to some extent regretted, but this was overwhelmingly counterbalanced by the thoroughness of the survey obtained.

Clinical and Pathological Descriptions

(Throughout the course of the several papers published on this material, it has been taken as a convention that each case is designated by the first three letters of the patient's name to simplify reference from one paper to another. This convention is continued.)

Case 1 (MIE)

As a child he had "eczema" at 18 months and attacks of asthma from the age of 7 years. Epilepsy began at the age of 12 years, the fits consisting predominantly of emotional, abdominal and penile sensations. Complex automatic manœuvres occurred during these auras of which the subject was unaware. There were also *grand mal* attacks once or twice a year. He had an inadequate personality, but his intelligence was normal.

When examined at 23 years of age there were no neurological abnormalities. The E.E.G. recordings showed a focus of abnormal activity over the right temporal lobe which on corticography at operation was localized to the uncus. The left temporal horn was seen in air encephalograms to be slightly dilated. The family history showed no examples of nervous disorder.

In the right temporal lobe after fixation was found a firm grey area containing several small cysts lying lateral and anterior to the amygdaloid complex. Serial sections of the lobe revealed this area to be made up of irregular contiguous cellular nodules (figs. 1 and 2) occasionally separated, especially anteriorly, by small (2 mm.) cystic spaces. The nodules varied in their cellular composition. The majority were made up of nerve cells of fairly normal appearances and containing sometimes abundant Nissl substance, separated by irregular groups of astrocytes and oligodendroglial cells, and often set in a pale blue-staining (cresyl violet) vacuolated matrix. Neither of the latter types of cells

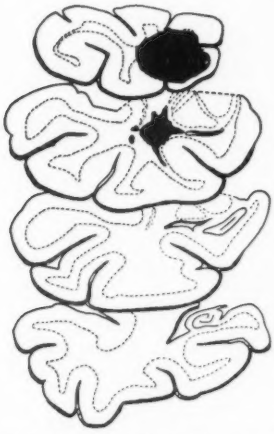

FIG. 1.—The topographical distribution of the tumour in Case 1 is indicated in black.

was for the most part demonstrably abnormal and the astrocytes largely resembled hyperplastic reactive forms. Occasional astrocytes with considerably enlarged bilobed or reniform nuclei of distinctly abnormal character were, however, seen.

Other nodules showed no nerve cells but only oligodendroglia and astrocytes, while one discrete cluster was composed almost wholly of oligodendroglia (fig. 3) together with several small calcospherites and numerous delicate capillaries. The latter areas, particularly the last, resembled on a small scale the tumorous masses of Cases 7 and 8. There was no suggestion of invasive activity and the nodules were confined to the white matter except anteriorly where they encroached upon the cortex of the temporal pole. Gliosis of the amygdaloid complex was conspicuous but it was without evident reduction of the neuronal population. There were no other abnormalities of significance in the remainder of the lobe.

Case 2 (LIB)

A lad of 16 years had been suffering from epileptic seizures since the age of 4 years. These were mainly akinetic attacks associated with tickling in the tongue and epigastric sensations; they occurred once to four times each week. *Grand mal*, sometimes spreading from around the face and mouth, occurred also about twelve times a month. Since the age of 7 he had exhibited a hyperactive behaviour disorder and had been backward and aggressive. His I.Q. was found to be between 60 and 70. There were no examples of mental disease discovered in the family history.

Examination revealed the right side of the body to be slightly smaller than the left, particularly the right arm. He was left handed. Air encephalograms demonstrated a slight atrophy of the left cranium and its contents; correspondingly the left temporal horn was found to be dilated and showed irregular indentations into its wall anteriorly. E.E.G. showed spike activity over the left mid-temporal zone.

At operation a cystic cavity was encountered in the anterior region of the temporal lobe, while, medial to this, grey, rather mucinous, tumour tissue involved the greater part of the pole and reached to the ventricle.

In the specimen the naked eye tumour-like tissue was found to occupy the greater part of the pole and the region of the amygdala (fig. 4). Laterally there was a collapsed cyst that reached out to the cortex while posteriorly the white matter around the ventricle

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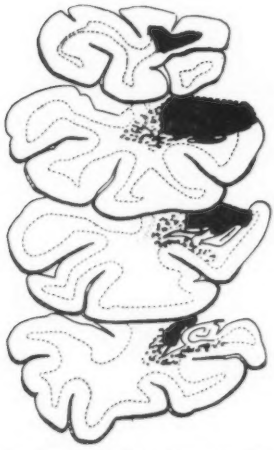

FIG. 4.—The extent of the tumour in Case 2 is shown in black and its further infiltration in stippling.

was firmer than usual. The Ammon's horn was enlarged, white and extremely firm; its normal grey and white zones were lost.

Paraffin-embedded tissue from the tumour anteriorly showed it to be composed of irregularly arranged nerve cells and neuroglia often separated by a mucinous vacuolated matrix (fig. 5). The nerve cells frequently contained abundant Nissl material while others showed chromatolytic changes. No monster cells were seen. Both astrocytes and oligodendroglia were represented, the former in greater numbers and not readily distinguishable for the most part from reactive forms. Scattered throughout were focal collections of small round cells of inflammatory type. The cyst was lined by reactive hyperplastic astrocytic cells.

Celloidin sections of the rest of the lobe revealed the changes to be more widespread than judged with the naked eye. The amygdala was virtually destroyed by the mass described above except for a portion of its posterolateral region; the uncus was affected antero-medially, while its pyramidal band was the seat of extensive calcospherite deposition. Laterally, adjacent to the ventricle, the tumour ran into a large collection of cells of a different character. These were undoubted astrocytic forms with large, often double, nuclei and abundant somewhat hyaline cytoplasm (fig. 6). These cells resembled the astroglial cells that compose the paraventricular nodules of tuberous sclerosis. Running medially from the posterior end of the tumour into the white matter of the hippocampal gyrus many of the astrocytic forms showed considerable pleomorphism of their nuclei. The cortex of the hippocampal gyrus was severely damaged by calcific deposits and glial proliferation. No monster cells, either neuronal or neuroglial, could be found in the neighbourhood of the tumorous masses or in the cortex elsewhere in the temporal lobe.

The Ammon's horn showed typical sclerosis of severe degree, the h_1, h_3 and h_5, regions of the pyramidal band being destroyed and the dentate fascia badly damaged, while the h_2 sector showed a moderate number of surviving neurones. The cortex throughout the rest of the lobe showed no laminar neuronal atrophy.

Comment.—These 2 cases are grouped together because of the basic similarity of the major parts of their tumorous masses, both of which

lie in close relation to the roof of the ventricle and the amygdala. They are heterogeneous and made up of mixed nerve cell and neuroglial formations; the nerve cells not being markedly abnormal in Nissl preparations and the astrocytes resembling for the most part reactive forms. Oligodendroglia was more conspicuous in the first case than in the second. Differences between them were, however, clear, not only on the microscopical level but also in their historical background. Thus, in Case 1 there is little or no evidence of invasive activity or neoplastic change. All the usual attributes of a malignant tumour are absent and, moreover, there is a conspicuous tendency for the cell clusters to be arranged in discrete groups, a feature that is less prominent in Case 2. In addition, the latter shows a feature suggesting the possibility of coexistent tuberous sclerosis in the presence of somewhat characteristic neuroglial cells in the subependymal region. The Ammon's horn sclerosis is a further provocative complication.

In contrast to their fairly similar pathological states, the clinical background of the 2 cases is quite the opposite. Case 1 was a man of normal intelligence, though with an inadequate personality, and the family background and physical condition of the patient had none of the stigmata of hereditary disease. Case 2, on the other hand, had a severely lowered intelligence and a distinct unilateral hypoplasia of the body, both signs of cerebral changes beyond the confines of the temporal lobe.

The long history and the mixed neuronal and neuroglial composition of the two tumours with relatively little evidence of neoplastic change cause them to resemble very closely the rare group of tumours collected and identified by Courville (1930, 1931, 1941) which he terms gangliogliomas. These are not common, estimated by him to form about 0·8 per cent of gliomas, but although they have been encountered throughout the neuraxis they show a striking predilection for the floor of the third ventricle and to a lesser degree the anterior temporal lobe. Of the 55 examples collected by Courville and Anderson up to 1941 no fewer than 17 were in relation to the wall of the third ventricle and 9 in the temporal lobe. A long history of epileptiform seizures in adolescents and young adults often with psychomotor features is rather typical of the temporal lobe group as shown, for instance, in the cases of Schmincke (1910) and Bielschowsky and Henneberg (1928). Usually the tumour is described as being "about the size of a walnut" and is closely related to the roof or floor of the lateral ventricle. Courville regards these tumours as being derived from cells of a bipotential nature and capable of ultimate transformation into polar spongioblastomas.

The unusual feature about Case 2 is the suggestion given by the clinical signs that a defect exists outside the temporal lobe. The clue to the nature of these more widespread changes is clearly given by the Ammon's horn sclerosis, which suggests that vascular or anoxic episodes, possibly connected with the *grand mal* attacks, may well have been responsible.

XUM

Case 3 (MUN)

While serving as an army officer, he began ten years previously at the age of 23 years to suffer from "blackouts" lasting only 2–3 seconds and occurring once or twice daily. These were accompanied by epigastric sensations and a feeling of detachment. Certain automatic actions occurred during the "absences" and chewing movements were also observed, but the patient had no memory of these events. Apart from a mild psychosexual character disorder, his personality was not affected. His I.Q. was rated at 138. There was no *grand mal.*

EEG recordings showed right fronto-temporal spike discharges and corticography during the operation localized these to the temporal pole and the uncus. Air encephalograms suggested a slight atrophy of the right hemisphere and of the ipsilateral temporal horn. No family history of epilepsy or mental disease was elicited.

During the operation firm tumour-like tissue was encountered in the medial and anterior regions of the temporal lobe and in the region of the amygdala. A small portion, removed and sectioned in paraffin, consisted of oligodendroglial cells set in an œdematous mucinous matrix together with a few nerve cells and hyperplastic astrocytes. No abnormality was seen in the rest of the temporal lobe when it was examined with the naked eye after fixation.

Microscopically serial sections demonstrated the presence of four separate and discrete lesions (fig. 7):

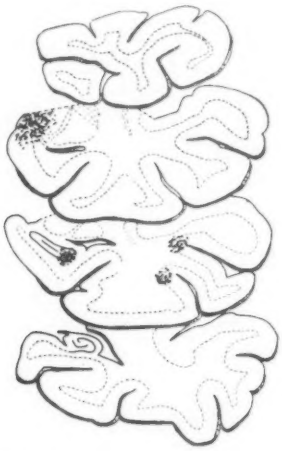

FIG. 7.—The four sites of tumour in Case 3 are shown in stippling.

(1) In the most medial regions of the amygdaloid complex, the corticotransitional region, at the excision edge there was a considerable increase in neuroglial cells, mainly oligodendroglia with a good admixture of astrocytes. This apparently tumorous tissue mingled with the local neuronal population and although there was marked satellitosis there appeared to be very little loss of nerve cells.

(2) In the Sommer sector of the uncus astride the pyramidal band was a sharply demarcated patch (fig. 8) of increased numbers of astrocytes with small nuclei and delicate cytoplasmic extensions (fig. 9). The nerve cells appeared to be in normal numbers.

(3) and (4). In the inner layers of the cortex at the base of the collateral sulcus and

the inferior temporal sulcus were two discrete nodules of neuroglial cells (fig. 10). These were oligodendroglial cells with clear perinuclear halos and a pronounced tendency either to form long columns of from 10–16 nuclei or to encrust the neurones thickly to the extent of more than ten cells to each neurone. Astrocytes were inconspicuous in these two foci but there was a curious intensity of staining in cresyl violet preparations of the intercellular matrix around the foci that was not further stainable with either mucicarmine or by the PAS procedure.

Apart from a slightly excessive amount of macroglia in the end-folium of the uncus and Ammon's horn and a moderate general subpial gliosis, no abnormality was encountered elsewhere in the lobe.

Case 4 (STA)

From the age of $5\frac{1}{2}$ years, fourteen years previously, akinetic attacks were observed apparently accompanied by a sensation of taste and frequently followed by unconsciousness. Such attacks occurred once or twice a day. At the same period there developed an anti-social change in the child's behaviour. The boy was institutionalized from an early age because of mental defect and his I.Q. was rated at 64. No abnormalities were found on physical examination but air encephalography indicated a small space-occupying lesion in the temporal pole. Furthermore, irregularities were seen in the floor of the right lateral ventricle that were reminiscent of the "candle guttering" appearance of tuberous sclerosis. There were no indications of this disease in the family, but a distant connexion was reported to have had mental deficiency and progressive muscular atrophy. EEG recordings showed three foci of spike activity, a major one over the right temporal convexity and two minor ones from the left and right sphenoidal leads.

To the naked eye after fixation the medial and anterior regions of the temporal lobe especially the amygdala and the uncus were grey, swollen and somewhat soft. Serial sections in celloidin revealed that these latter regions (fig. 11) were greatly distorted by the presence of large numbers of oligodendroglial cells (fig.12) with small darkly-staining and regularly rounded nuclei and conspicuous perinuclear halos. Short processes were demonstrable in many of these cells by silver impregnation. Their arrangement was not

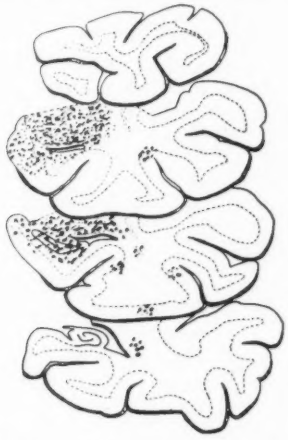

FIG. 11.—Case 4. Stippled areas indicate sites of main tumour and additional small tumour masses.

XUM

uniform, for frequently they formed long parallel rows or small clumps with a central astrocyte. Wherever possible there was pronounced satellitosis of nerve cells. In many areas a vacuolated mucinous matrix occurred, which failed to stain, however, either with mucicarmine or with the PAS procedure.

Apart from this larger mass there were several smaller clusters of oligodendroglial cells scattered in the depths of the cortex of the fusiform, inferior temporal and middle temporal gyri (fig. 13). They were separate and discrete and in all respects were identical with those described in Case 3 (MUN), even to the extent of showing the intensely staining intercellular background.

In the roof of the temporal horn and lateral to the tail of the caudate nucleus was a small cluster of abnormal and sometimes enlarged astrocytic cells. Several of these had double or bizarre-shaped nuclei and showed abundant cytoplasm (fig. 14). Other cells took up elongated or spindle forms. They appeared somewhat akin to the paraventricular astrocytic clusters encountered in tuberous sclerosis. No giant or monster cells were, however, found in this or any other part of the temporal lobe.

Comment.—Cases 3 (MUN) and 4 (STA) from a pathological standpoint are closely allied, not only by reason of the predominantly oligodendroglial nature of the tumorous nodules and their multifocal character, but also in virtue of the associated astrocytic collections which were in both instances entirely separate formations. Despite these apparent similarities, as in the first pair of cases, the differences in their backgrounds is pronounced. Case 3 (MUN) was a man of normal or high intelligence without family history of mental disturbance, in fact with none of the stigmata that characterized Case 4 (STA) as a possible example of tuberous sclerosis in an incomplete form. If the diagnosis in the latter is correct, this example is unique in the records of this condition in being associated with an oligodendrogliomatous formation. According to Hallervorden and Krücke (1956) oligodendrogliomas have not been found in tuberous sclerosis; gliomatous changes are of spongioblastic type, and spring, for the most part, from the paraventricular neuroglial nodules (Globus, 1938, among others). Whether the astrocytic nodule was a lesion of this character must remain uncertain; even more uncertain is the nature of the glial nodule across the pyramidal band of Case 3 (MUN). There were certainly no other suggestions of this condition in this patient. In such a protean disease (Critchley and Earl, 1932; Moolten, 1942) one must beware of too readily dismissing the possibility of the existence of a minor form both in Case 1 and in Case 3. Normal or even fairly high intelligence is not unknown among the siblings of overt cases even though these may show isolated minor manifestations of the condition. That the siblings have never been the subject for detailed study is a regrettable lacuna in our knowledge of the *formes frustes* of tuberous sclerosis. Even in overt cases cortical lesions may be few or sometimes solitary, as was found by Jakob (1914) and Yakovlev (1939).

Case 5 (MAR)

A male aged 32 years at operation; he had suffered from minor epileptic seizures for the past thirteen years with a frequency of from two to three each day. These

fits consisted of periods of mental "absence" lasting 5–10 seconds during which time he was unable to speak; he had a sense of groping for something out of reach of his memory, but he had no bodily sensations. Major seizures, involving the right side of his body only, also occurred about once a month.

Radiography revealed a slightly but uniformly dilated left lateral ventricle. EEG showed sharp spikes of long duration over the left mid-temporal region. His character and intelligence were normal and there was no family history of mental disease.

The operative specimen was somewhat hæmorrhagic from handling, especially in the area subsequently found to contain a small tumorous nodule.

Microscopically there was a cellular nodule expanding the middle part of the fusiform gyrus and occupying the overlying cortex as well as the greater part of the white matter (fig. 15). The cortex at the sides of the gyrus was involved also, but the laminar architecture was not greatly disarranged.

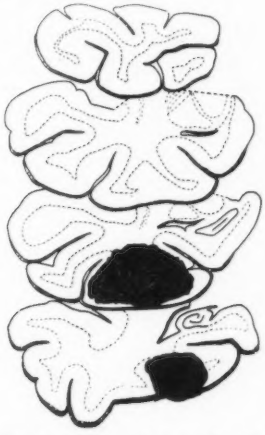

FIG. 15.—Tumour (in black) in Case 5 is confined to the fusiform gyrus.

The tumour consisted, for the most part, of closely packed cells which from their regularly rounded nuclei and their clear perinuclear haloes were recognizable as oligodendroglial cells. They were especially typical in their appearances where they lay beneath and were beginning to invade the overlying pia mater. Also present in the centre of the nodule were a moderate number of cells with scanty cytoplasm and much larger oval or bean-shaped nuclei. Similar large cells were found in the cortex on either side of the nodule and in this situation they were frequently seen to be clustered around neurones in the manner of satellites. Quite apart from the tumour mass, lying in the cortex of the collateral sulcus and the inferior temporal sulcus, were clusters of cells similar to those described above accompanied by hypertrophic reactive astrocytes (figs. 16 and 17). In form, content and position these latter formations were reminiscent of the clumps of blastomatous neuroglia that are frequently seen in the central form of von Recklinghausen's neuro-fibromatosis.

Additional features of the nodule were the presence of a number of minute cysts in its centre and abundant calcific deposits in the matrix and in the walls of small vessels in the cortex adjacent to the tumour. There were no abnormal features in the remaining parts of the temporal lobe beyond a mild increase in macroglia in the end-folium of Ammon's horn and beneath the pia generally.

XUM

Case 6 (VAL)

An otherwise healthy male, aged 22 years, had begun to exhibit minor seizures about two years earlier. Six months before this he had fallen from a horse and struck his head, but had only been dazed afterwards. The attacks occurred six to twelve times each day and consisted of a dreamy detached state lasting a few seconds, but during this time masticatory movements were observed and epigastric and "gooseflesh" sensations were sometimes felt. There were no abnormal sensations of taste or smell. His I.Q. was rated as "high" and there were no cases of mental disease in his family history.

Air encephalograms revealed a slight indentation in the lateral edge of the left temporal horn. EEG recordings showed the presence of slow waves and spikes emanating from the left fronto-temporal regions.

When the temporal lobe was received it was noted that the cortex of the fusiform gyrus was adherent to the meninges in what was considered to be a cicatrix. Serial sections made it evident, however, that these adhesions overlay a small but cellular tumour which largely occupied the fusiform gyrus and had destroyed its superficial cortex (fig. 18). Outwardly the tumour was infiltrating the leptomeninges, while within it

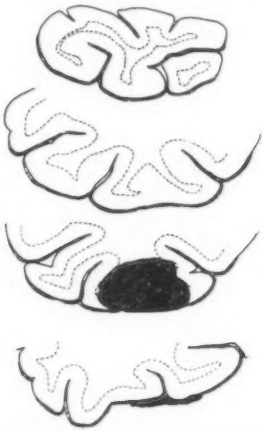

FIG. 18.—Tumour (in black) in Case 6 in the fusiform gyrus.

was beginning to invade the white matter around the collateral and inferior temporal sulci. The main cellular component of the tumour was a bipolar spongioblast (fig. 19), but showing little structural arrangement except for a slight tendency to group around small blood vessels. Near the outer surface of the tumour, the cells had a distinctly pleomorphic aspect and several multi-nucleate forms were seen. Pleomorphic forms were also encountered in the white matter deep to the tumour.

Separated from the tumour by apparently normal cortex were several small clusters of grossly abnormal neuroglial cells (fig. 20), the groups being readily recognizable with low magnifications. They were made up of ill-organized collections (fig. 21) of hyperplastic astrocytes and "blastomatous" forms with enlarged and bizarre nuclei. As in Case 5 they were reminiscent of the cortical cell clusters encountered in von Recklinghausen's neurofibromatosis. There were no other abnormalities detectable in the remainder of the temporal lobe. Ammon's horn, uncus and amygdala were not present in the specimen.

(This case has been included in previous publications of this series of temporal lobectomies under the tentative diagnosis of meningioma. On review of the material this diagnosis could not be upheld in view of the largely intracerebral position of the nodule, the almost complete absence of reticulin fibres in its substance, the markedly pleomorphic form of many of its cells and the occurrence of glial fibrils in the Mallory preparations. These appearances taken in conjunction with the clusters of abnormal neuroglial cells in the adjacent cortex, quite apart from the tumour, would strongly suggest that it is of neuroglial origin.)

Comment.—These two examples show few real differences between them; only the nature of the component cells and the length of the epileptic history. Both are in essence instances of small incipient subcortical neuroglial tumours of the fusiform gyrus at a stage of such limited extension as not to have destroyed distinctive clusters of abnormally formed glial cells in the adjoining but otherwise uninvolved cortex. In Case 5 (MAR) similar cells appeared to take part in the tumour; in Case 6 (VAL) they were of quite different appearance to the tumour cells. They were similar to Alzheimer type II glia which, although recognized as not specific for the condition, are typically encountered in the central form of von Recklinghausen's neurofibromatosis, in which condition numerous clusters of such cells are to be seen scattered throughout the grey matter. This genetic abnormality which is conferred probably by a dominant hereditary mechanism (Borberg, 1951; Crowe, Schull and Neel, 1956) and has a high mutation rate (Crowe, Schull and Neel, 1956), is well known to exhibit incomplete forms in the manner of tuberous sclerosis. No general disease was apparent in these two patients nor was there evidence of a familial trait towards this condition. The exact significance of the cortical clusters of aberrant cells must, therefore, remain in doubt.

(Cases 7 and 8 have been published in detail both from clinical and pathological aspects by Falconer, Pond, Meyer and Woolf (1953). Although no new points have emerged from a reassessment of the lesions, they are included here in brief, mainly because in the light of the findings in the other six tumorous cases which came later in the series it would seem reasonable to reorientate our ideas with regard to the nature of these two earlier cases. They were provisionally placed into the category of "hæmangioma calcificans," which category would now appear to be unsuitable for the reasons given below.)

Case 7 (SIN)

A girl, aged 26 months at operation. After normally developing for the first 14 months, she began to be irritable and fretful, often showing outbursts of temper for no reason. At the age of 2 years, minor seizures, characterized by periods of vacancy and purposeless movement of the arm and head, began to occur and became as frequent as six to eight times each day. The character disturbance seemed to improve temporarily with the onset of the fits, but normal development ceased from that time. No *grand mal* occurred. One cousin was said to have temper tantrums, hallucinations and an abnormal EEG.

XUM

Air encephalograms showed a partly calcified lesion lying beneath a slightly dilated trigone on the left side. EEG recordings revealed irregular spike and wave discharges over both hemispheres.

At operation a mass was found beneath the ventricle in the posterior third of the left temporal lobe, which was excised. The specimen included the inferior temporal, the fusiform and part of the hippocampal gyri (fig. 22), but not the pole, the uncus or th cornu ammonis.

FIG. 22.—Case 7. Tumour (in black) occupying the middle two blocks of the standard diagram, showing its extent by comparison with the rest.

The microscopic appearances were those of a tumour occupying the white matter of the above gyri, the most striking features of which were large numbers of calcareous granules and numerous cystic spaces. The tumour tissue proper was composed of an intimate mixture of astrocytes of relatively normal but hyperplastic type and oligodendroglia (fig. 23), the latter frequently preponderating and it was difficult to decide in any one area whether the astrocytic element was an essential part of the tumour or a reactive phenomenon. There were numerous delicate capillaries present throughout the tumour, but no larger vessels. The microcysts were lined by neuroglial tissue. Where the tumour involved the cortex, it had caused considerable disorganization and gliosis, but there were no nerve cells forming part of the tumour. No clusters of abnormal neuroglia were visible in the remaining intact parts of the cortex available.

Case 8 (KIE)

A girl, aged 14 years, who at the age of 9 began to have fits which commenced as strange abdominal sensations, after which she would go into a dazed state and concluding with a brief period of unconsciousness. These episodes continued with increasing frequency until about a year after their onset, when her behaviour began to deteriorate so markedly as to necessitate her removal for short periods to institutions. Her I.Q. was rated at 79 on the Weschler Full Scale, but no physical or neurological abnormalities were found on examination.

Air encephalograms showed the right lateral ventricle to be slightly smaller than the left. Irregular sharp-and-slow complexes were detectable in the EEG over the right fronto-temporal regions.

There was little abnormal visible to the naked eye in the specimen, but serial celloidin sections showed a tumour-like mass containing an abundance of calcospherites lying in the posterior amygdaloid region and in the uncus (fig. 24). Medially the mass was in contact with the meninges. The component cells were an intimate mixture of astrocytes and oligodendrocytes (fig. 25), their proportions varying from one area to another. Many delicate capillaries ran through the tumour, but no larger vessels were found, and no cystic spaces. Although several cells with enlarged and bizarre nuclei were identifiable in the tumour, there was little other evidence of pleomorphism and there were no abnormal glial cells in the cortex elsewhere in the lobe.

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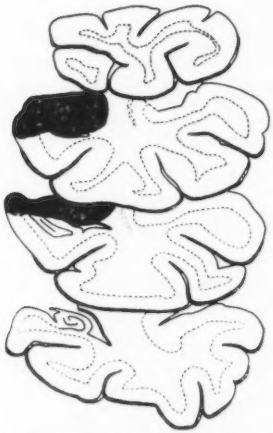

FIG. 24.—Case 8. Extent of the tumour is indicated in black.

Comment.—The final pair of cases are strictly comparable in their cellular make-up, although they differ in situation and in their time-relationships. They are included in this study because of the early age of their appearance, the mixed nature of the tumours and their evidently benign aspects which suggest that they may be in the nature of hamartomas. In the original publication (Falconer *et al.*, 1953) the nosological position of the two tumours was deliberately left uncertain and they were tentatively classed as "hæmangioma calcificans", largely because of the striking degree of calcification present. It is clear from Penfield and Ward's (1948) paper on the subject, however, that large and thick-walled vessels are to be taken as an essential component of such a lesion, a feature not conspicuous in these two tumours. On review, therefore, by virtue of the mixed neuroglial nature of the tumours and the occasional presence of pleomorphic forms in Case 8, it would seem to be more natural to class them as gliomas of benign aspect, either related to the oligodendro-astrocytoma of De Busscher and Scherer (1942) or possibly hamartomatous. The microcyst formation in Case 7 and the excessive calcification of the intercellular matrix in both would not be incompatible with this view. It is of interest that somewhat similar mixed astro- and oligodendroglial nodules were a particular feature of Case 1 (MIE).

DISCUSSION

One of the most difficult questions to answer is whether these tumours or tumour-like formations do or do not show malignant change. Except in Case 6, with undoubted invasion of the pia, none of the usual histological criteria can be of assistance, and the only really valid indication, namely evidence of steady growth given by corresponding increase in symptoms,

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is wanting. Moreover, there has been no evidence of tumour recurrences during the one to seven year follow-up of these patients (Table I), while the long epileptic history in 6 out of the 8 cases would further suggest their essentially benign nature, at any rate up to quite shortly before operative interference. Furthermore, the clinical history of more than ten years in the majority might be taken to indicate that these formations arose in fact at some unspecified time before the epilepsy was first observed, perhaps during the final stages of cellular proliferation and differentiation of the infant brain. The observation that the greater number were closely related to the ventricular wall might even suggest that they were derivatives of the mantle layer from which the tissues of the cerebrum are derived, that is hamartomas in the sense first used by Albrecht (1904). Such a view is commonly accepted for the original of the paraventricular nodules of tuberous sclerosis, for instance (Yakovlev, 1939), in which clinical phenomena do not usually develop until the second half of the first decade and sometimes not until the second, third or even the fourth decade, as in one recent unpublished instance of our own. Yet there is little cytological evidence of persistence of the mantle zone after the first year of extrauterine life at the latest.

Practically nothing is known of the origin of gliomas, and by comparison with the huge volume of experimental work on non-nervous neoplasms virtually nothing, outside the interesting experiments of Zimmerman (1955), has been done on the nervous system. This is the more surprising when it is considered that some of the possible mechanisms that may be operative in other tissues probably cannot be transferred validly to nervous tissue in view of the apparently extremely limited cellular replacement normally in progress in the adult brain. Any such mechanism in which genetic factors are implicated, such as is envisaged in the somatic mutation hypothesis in its broadest sense, is unlikely in the brain unless a persistent focus of mitotic activity is present. There is even uncertainty as to whether mature astrocytes divide by mitosis, and such experienced observers as Hortega and Penfield (1927) and Courville (1950) have declared that these cells reproduce by a process of amitotic division, a process that cannot conceivably be of much genetic significance if it exists at all in the healthy cell. Apart from possible cytoplasmic or viral mechanisms for which evidence is lacking, if these observations are acceptable, one is virtually forced to consider an alternative explanation along the lines of the classical Cohnheim theory of embryonic cell rests. Two approaches exist from this standpoint postulating either the persistence of cells with multiple potentialities for development and differentiation along neuroblastic and/or spongioblastic lines and capable of ultimate neoplastic transformation, or the occurrence of hamartomatous by-products of cerebral development which, because of their incomplete maturation, would be capable of progressive multiplication and subsequent malignant

TABLE I

Case No.	*Epileptic history*	*X-ray changes*	*Side removed*	*Site*	*Cellular components*	*Follow-up period*
1 (MIE)	11 years	L. temporal horn dilated	Right	Para-amygdaloid	Neurones. Neuroglia	3 years
2 (LIB)	12 years	Deformity of L. temporal horn	Left	Para-amygdaloid. Para-ventricular	Neurones. Neuroglia	6 months
3 (MUN)	10 years	R. hemisphere and temporal horn. Sl. small	Right	Medial amygdaloid. Collateral sulcus. Inf. temporal sulcus. Uncus	Neuroglia. (mainly oligodendroglia)	3½ years
4 (STA)	14 years	Irregular floor of R. temporal horn	Right	Amygdaloid and uncus. Hippocampal, fusiform. Inf. temporal cortex	Neuroglia (mainly oligodendroglia)	2 years
5 (MAR)	14 years	L. temporal horn dilated	Left	Fusiform gyrus	Neuroglia. (Oligodendroglia)	4 years
6 (VAL)	2 years	Sl. asymmetry of L. temporal pole	Left	Fusiform gyrus	Neuroglia. (Spongioblasts)	5 years
7 (SIN)	4/12 years	Dilated L. temporal horn. Calcification	Left	Posterior temporal	Neuroglia. (Oligo-astrocytes)	7 years
8 (KIE)	5 years	R. lateral ventricle small	Right	Amygdaloid uncus	Neuroglia. (Oligo-astrocytes)	6 years

change in response to further stimuli. The argument that such hamartomatous formations, if they existed more commonly, would be more frequently observed in otherwise normal brains is not valid in view of their sometimes very small size as shown by several instances in this series. Moreover, lest it be thought that the tumours in this series are fortuitously numerous, I have been assured by Dr. Maitland Baldwin that similar nodular collections of cells have been met with in about the same proportion of the temporal lobectomy series of the Montreal Neurological Institute, though they have not yet been the subject of detailed study.

The only firm conclusions, therefore, that may be drawn from this material at the present time is that their epileptic history suggests that they have been present in the majority for at least ten years and possibly since early childhood, that they may, therefore, be hamartomatous in nature, and that they may be considered as possible potential points for the further development of gliomas.

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Summary

A group of 8 cases of temporal lobe epilepsy associated with the presence of small nodular tumours in the temporal lobe have been described in detail. The majority had been present for many years and may have originated in early childhood. While they were considered as most likely to be hamartomatous formations, a few showed the earliest evidence of neoplastic transformation. Evidence suggestive of the presence of tuberous sclerosis was present in one example. Whether these tumours could be considered as potential sources of gliomas is briefly discussed.

Acknowledgments

I particularly wish to thank Professor A. Meyer for allowing me access to this material and for his stimulating interest.

Mr. Murray A. Falconer, F.R.C.S., was good enough to allow me full access to the clinical notes. My thanks are also due to Mrs. Edna Courtenay for preparing the abundant histological material, and to Mr. R. J. Passingham, of Guy's Hospital Medical School, for the photomicrographs.

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PLATE LV

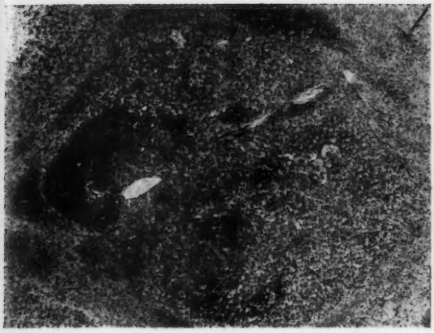
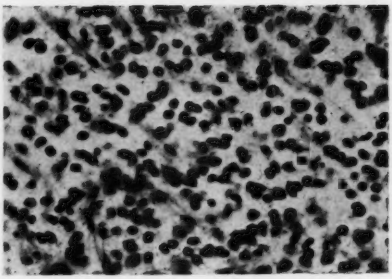


FIG. 2.



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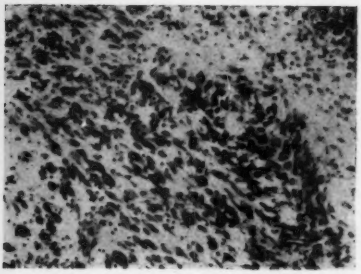

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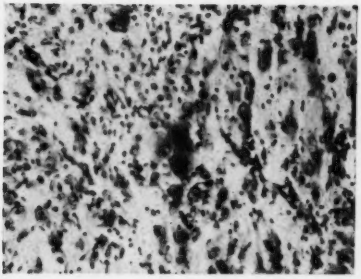

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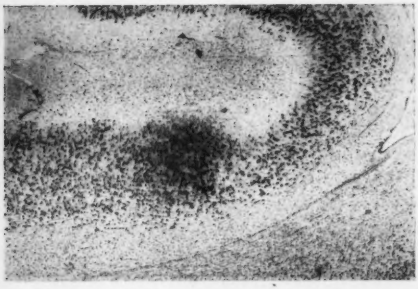

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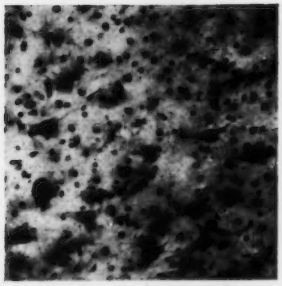

FIG. 9.

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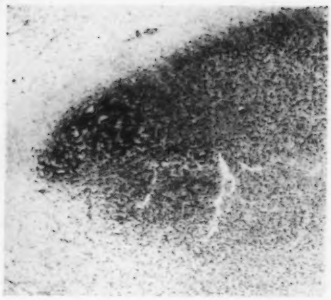
PLATE LVI



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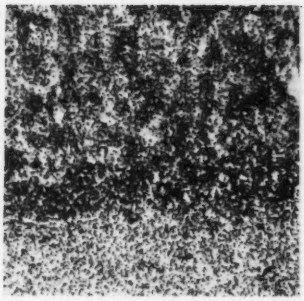

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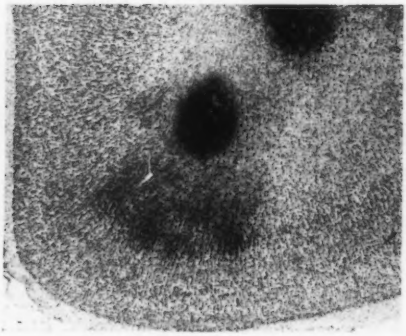

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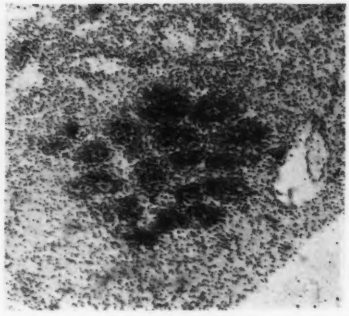

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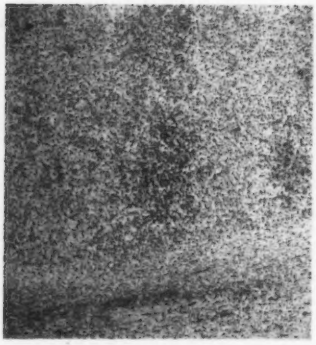

FIG. 16.

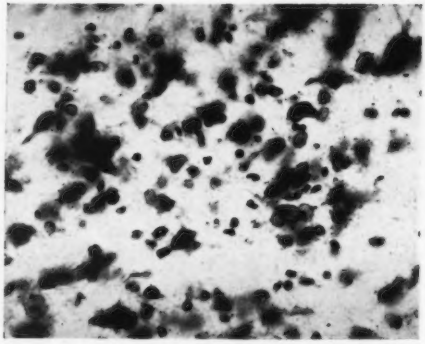

FIG. 17.

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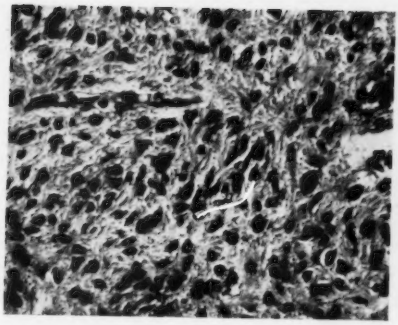
PLATE LVII



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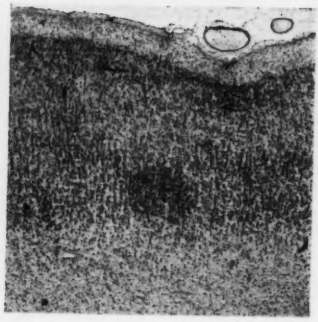

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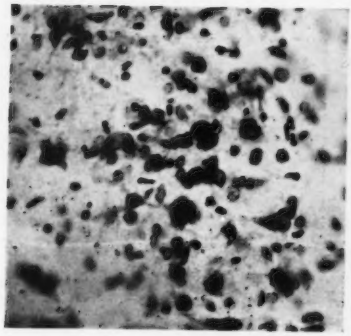

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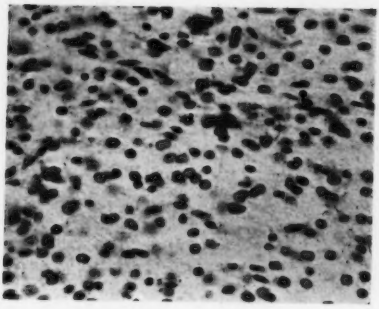

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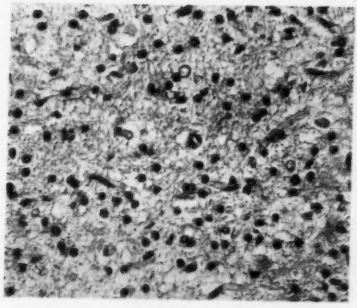

FIG. 25.

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LEGENDS FOR PHOTOMICROGRAPHS

PLATE LV

FIG. 2.—Case 1 (MIE). Tumour in the para-amygdaloid white matter. The dark areas consist of neuroglial (astro-oligodendroglial) cells; the lighter areas of neuronal elements and astrocytes. Cresyl violet. × 15.

FIG. 3.—Case 1 (MIE). Almost pure oligodendroglial area. Cresyl violet. × 900.

FIG. 5.—Case 2 (LIB). Clusters of nerve cells in the tumour. Cresyl violet. × 100.

FIG. 6.—Case 2 (LIB). Large plump astrocytes and two bizarre nuclei from paraventricular region. Cresyl violet. × 166.

FIG. 8.—Case 3 (MUN). Astrocytic nodule astride Sommer's Sector of the uncus. Cresyl violet. × 15.

FIG. 9.—Case 3 (MUN). High power of nodule in fig. 8 showing numerous hyperplastic astrocytic forms. Cresyl violet. × 900.

PLATE LVI

FIG. 10.—Case 3 (MUN). Oligodendroglial nodules in the depths of the cortex (obliquely cut) of collateral sulcus. Cresyl violet. × 15.

FIG. 12.—Case 4 (STA). Part of the main mass involving the pyramidal band of the uncus. Cresyl violet. × 65.

FIG. 13.—Case 4 (STA). Cortical and subcortical nodules of oligodendroglia in fusiform gyrus. Note the similarity to fig. 10. Cresyl violet. × 15.

FIG. 14.—Case 4 (STA). Paraventricular clusters of astrocytic forms. Cresyl violet. × 60.

FIG. 16.—Case 5 (MAR). Cluster of neuroglial cells in the cortex of the inferior temporal gyrus separate from the tumour. Cresyl violet. × 15.

FIG. 17.—Case 5 (MAR). High power of fig. 16 showing the abnormal cell forms. Cresyl violet. × 900.

PLATE LVII

FIG. 19.—Case 6 (VAL). The tumour showing the irregularly arranged spindle spongioblastic cells. Mallory. × 900.

FIG. 20.—Case 6 (VAL). A neuroglial cluster in the depths of the inferior temporal cortex. Cresyl violet. × 15.

FIG. 21.—Case 6 (VAL). A high power of the cluster shown in fig. 20. Cresyl violet. × 900.

FIG. 23.—Case 7 (SIN). Oligodendroglial and astrocytic forms in the tumour. Cresyl violet. × 350.

FIG. 25.—Case 8 (KIE). Part of the tumour to show the cell types. Cresyl violet. × 300.

All magnifications have been reduced by one-fifth during printing.

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EFFECTS OF TEMPORAL AND FRONTAL CORTICAL LESIONS ON AUDITORY DISCRIMINATION IN MONKEYS

BY

LAWRENCE WEISKRANTZ[1] AND MORTIMER MISHKIN[2]

Institute of Living, Hartford, Conn.

EVIDENCE has been accumulating in recent years which suggests strongly that cortical areas outside the primary sensory projection areas play an important role in the perceptual functions of monkeys. Thus, it has been found that bilateral inferotemporal lesions produce an impairment in visual discrimination learning (Chow, 1952; Mishkin, 1954; Mishkin and Pribram, 1954), and that posterior parietal lesions impair somesthetic discrimination learning (Pribram and Barry, 1956). Of considerable theoretical and methodological importance is the fact that these relationships tend to be mutually exclusive, i.e. the temporal lesion seems to produce little or no change in somesthetically guided behaviour and the parietal lesion little or no change in visually guided behaviour. These findings lead to the expectation that other sensory modalities may also have "non-primary" cortical areas with which they are uniquely associated. This paper reports the results of a preliminary search for such an area in audition. The area selected for study comprises that portion of the posterior "association" cortex which lies between the areas implicated in vision and somesthesis. The hypothesis tested is that ablating this posterior temporal region without damaging the adjacent primary acoustic area will produce impairment in auditory discrimination learning.

Two other related aims are incorporated in the experimental design. In the first place an attempt is made to test further the proposition that the posterior cortical foci already discovered serve functions that are modality specific. To this end animals with inferotemporal lesions were included in the study in order to determine whether such lesions would indeed fail to produce deficit in auditory discrimination learning. Secondly, an attempt is made to investigate the findings of Ades and his associates (Stewart and Ades, 1951) and Blum (1952) that dorsolateral frontal lesions,

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ordinarily associated with impairment in a special class of problem-solving (delayed-response-type) behaviour, produce deficit also in performance on certain auditory tasks. Animals with dorsolateral frontal lesions are included in the present study in order to permit a comparative estimate to be made of the effects of frontal as opposed to the effects of posterior cortical lesions.

Material and Methods

Subjects.—The subjects were 15 rhesus monkeys (*Macaca mulatta*). 6 were tested for post-operative learning; the other 9 were tested for post-operative retention.

In the *post-operative learning group* there were 2 subjects in each of the three operative categories: posterior temporal (PT), inferotemporal (IT), and lateral frontal (LF). Of the 6 subjects, 4 (IT–164, IT–178, LF–168, LF–171) had previously received post-operative testing on a visual discrimination. The others (PT–287, PT–285) were naive.

In the *post-operative retention group* there were 3 subjects in each of the three operative categories. One animal was in each operative category (IT–249, PT–248, LF–228) had received pre-operative training on another auditory problem which it had failed to learn. 8 of the 9 animals were operated two to five days after reaching the standard on the auditory task described below. The ninth animal (LF–275) was given a pre-operative retention test thirteen days after reaching the standard. After re-learning this animal was given an LF lesion and included in the LF retention group. Re-learning trials for all subjects were begun on the tenth day following operation.

Surgical procedures.—Animals were anæsthetized with Nembutal and surgery was performed under strict aseptic procedure. The lateral frontal and posterior temporal areas were exposed by turning a large bilateral bone flap (anteriorly for the frontal and posteriorly for the temporal exposures) on the left temporal muscle. The inferotemporal area was exposed by removing temporal bone. Cortical tissue was removed by subpial suction. Silk was used in suturing successive layers of tissue.

On completing the experiments animals were sacrificed and the brains were removed for histological processing. After the brains were serially sectioned and stained with thionine, the limits of the lesions were determined by microscopic examination and reconstructed graphically, and the thalamus was studied for evidence of retrograd degeneration.

Fig. 1 shows such reconstructions, together with representative cross sections and thalamic sections, for the five PT lesions. In general these lesions extended from the lunate sulcus, posteriorly, to the tip of the intraparietal sulcus, anteriorly; and from the intraparietal sulcus, dorsally, to the tip of the inferior occipital sulcus, ventrally. All the lesions spared the supratemporal plane of the Sylvian fissure and there is no evidence of retrograde degeneration in the medial geniculate bodies. However, four of the five PT lesions produced degeneration in the central portions of the lateral geniculate bodies, probably as a result of unintended damage to the radiation fibres below the cortex. Degeneration in portions of the inferior and lateral nuclei of the pulvinar is due, according to Chow (1950), to ablation of the posterior temporal and inferior parietal regions.

The IT and LF lesions both resembled lesions made in a large number

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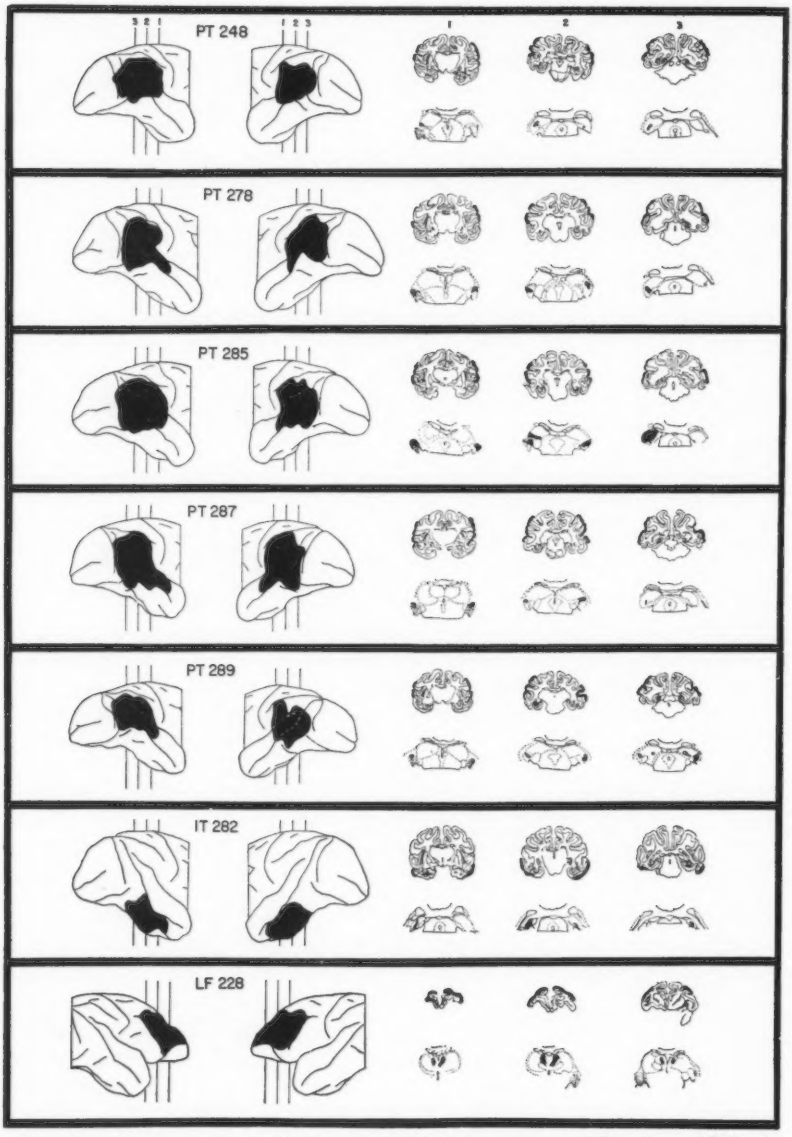

FIG. 1.—Reconstructions of lesions in all PT brains, and one IT and one LF brain. Representative cross sections and thalamic sections are shown to the right.

of studies from this laboratory (e.g. Pribram and Mishkin, 1956). For purposes of comparison with the PT lesions, reconstructions of one inferior temporal and one lateral frontal lesion are included in fig. 1. The IT lesion extended dorsally to include the inferior bank of the superior temporal sulcus and ventrally to include the fusiform area. The pole was spared anteriorly while the tip of the inferior occipital sulcus marked the posterior limit. Retrograde degeneration was found in the posterior portions of the medial pulvinar. The LF lesion extended posteriorly to the arcuate sulcus (including its anterior bank), dorsally to the longitudinal fissure, and ventrally to the lateral lip of the orbital surface. Both banks and the depths of the sulcus principalis were removed. The medialis dorsalis nucleus was largely degenerated.

Training procedure.—The auditory task consisted of training subjects to discriminate a white noise from a pure tone of 1,000 cps. These stimuli were generated by a Grayson-Stadler twin-oscillator unit, and were delivered through a 6 in. speaker placed horizontally 1 ft. above the testing cage. The intensity of the stimuli was set at 16 db. on the instrument, a value which was estimated to be 35–40 db. above the noise level of the testing room.

During the experimental session the animal was placed in a cage in a sound-proofed room which also contained a ventilator that served as a masking-noise generator. All stimulus and reward events were controlled automatically by relay and timing equipment in an adjoining room.

The discrimination was established according to a set of contingencies described elsewhere (Weiskrantz, 1957, Section V). Briefly, the stimuli were presented successfully in a predetermined balanced sequence which was varied daily. Each stimulus had a duration of 5 seconds unless the animal turned it off sooner by pressing a panel mounted on the front of the cage. If the stimulus was white noise the animal could obtain a pellet of food by pressing the panel. If the animal did not press during the white noise, but allowed it to go off automatically after the 5 seconds, then the white noise was repeated on succeeding runs until the animal did turn it off and received the reward. Conversely, if the stimulus was a 1,000-cps. tone the animal could obtain food only by *refraining* from pressing the panel. If the animal turned off the 1,000-cps. tone it was repeated on succeeding runs until the animal let it go off automatically, at which time a food pellet was delivered. Each food delivery was accompanied by a light over the food dish (located below the panel) which remained on for 2·5 seconds. There was an interval of 5 seconds between the termination of one stimulus and the beginning of the next unless the animal was rewarded, in which case there was a 5-second interval between the end of the reward period and the presentation of the next stimulus.

Twenty noise and twenty tone trials were delivered daily, excluding

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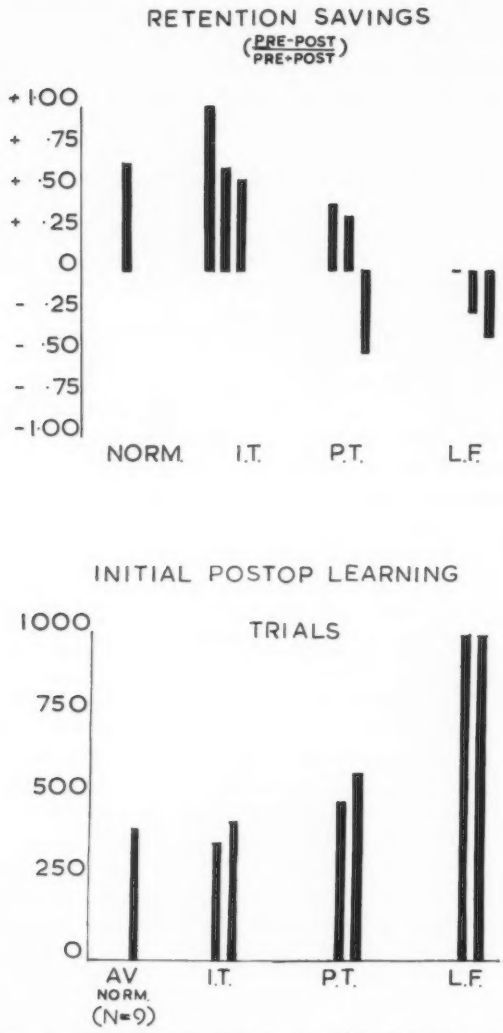

FIG. 2.—Pre-operative and post-operative learning and performance scores.

re-runs after errors, until the animal achieved 90 per cent correct out of the 40 daily trials on two successive days.

Preliminary training consisted of first teaching the animal to press the panel for reward, and then to press the panel only during the presentation of the white-noise stimulus. When the animal had reached a criterion

of responding to at least 40 out of 44 white noise presentations and of responding not more than ten times in the "silent" intervals between these 44 presentations, it was given the discrimination task using both auditory stimuli.

RESULTS

Initial post-operative learning.—Post-operative learning scores are shown graphically in the *lower* half of fig. 2. There is no overlap among the scores for the 3 operative pairs. The 2 IT subjects fall symmetrically on either side of the control average (computed from the pre-operative learning scores of the 9 animals tested for post-operative retention). The PT subjects required more trials than the IT subjects. The LF subjects did not solve the problem within the 1,000 trials allotted.

Post-operative retention.—The retention scores are shown graphically in the *upper* half of fig. 2. They are computed from the pre-operative and post-operative scores, listed in Table I, by the formula: No. of

TABLE I.—PRE-OPERATIVE AND POST-OPERATIVE LEARNING AND PERFORMANCE SCORES

Animal	*Pre-operative trials*	*Post-operative trials*	*Average performance 200 trials Post-criterion*
IT–249	280	80	95·5%
IT–282	280	0	95·5
IT–288	560	120	96·0
PT–248	200	600	92·0
PT–278	400	160	96·5
PT–289	880	440	88·5
LF–228	160	400	88·5
LF–283	360	360	87·0
LF–275*	(120)	200	92·0
C–275*	560	120	—

*This animal was first tested for pre-operative retention (*see* text).

pre-operative trials minus No. of post-operative trials divided by the sum of pre-operative and post-operative trials. A score of zero would indicate that pre-operative and post-operative scores are the same; positive scores indicate savings in relearning while negative scores indicate retardation in relearning. The measure can vary from plus 1·0 to minus 1·0.

There is no overlap between the IT subjects (all of which showed a high positive retention score equivalent to that shown by the normal control) and either of the other two groups of operated animals. Of the

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latter two groups, those with the LF operation were the more severely impaired. All their retention scores are negative indicating that all frontal animals required more trials to re-learn after operation than they had required initially. 2 of the 3 PT animals' scores, on the other hand, are positive. The last column of Table I lists the performance of each animal during the 200 trials immediately following the attainment of criterion. Although there is overlap among the three groups, the rank order in terms of average group performance is, again, IT, PT, and IF.

Discussion

Inferotemporal lesion.—Neither in initial learning nor in retention was there any suggestion of a difference between the animals with inferotemporal lesions and the normal controls. This finding provides new evidence for the hypothesis that inferotemporal lesions produce a behavioural deficit limited to discrimination learning in vision.

Lateral frontal lesion.—The results obtained with the animals with dorsolateral frontal lesions supports earlier findings of deficit in auditory discrimination learning following frontal damage. Both in initial learning and in retention all animals with lateral frontal lesions were severely impaired. Superficially, at least, such a finding falls outside the class of phenomena usually associated with lateral frontal lesions in monkeys, viz., deficit in delayed-response-type tasks.

Two lines of attack are evident for future research. Firstly, one might suggest that performance on auditory-discrimination tasks and on delayed-response tasks is impaired by lesions having independent and spatially separate foci, and that the lateral frontal lesion includes both. According to Sugar, French and Chusid (1948) there are strong connexions in monkey between the primary auditory cortex and area 8, a strip located at the posterior limit of the lateral frontal lesion. It would not be surprising to find a cortical area far removed from the primary acoustic area serving discrimination functions in audition. The inferotemporal region, which appears to fulfil such a role in vision, is quite distant from the striate cortex (although no analogous connexions between the striate cortex and the inferotemporal region are yet known).

Another possibility, however, is that the lateral frontal lesion is interfering with a *single* class of behaviour. While the theoretical task of uniting auditory discrimination learning and delayed-response-type learning appears formidable, certain lines of experimental approach may be suggested. For example, one possible critical difference between the auditory discrimination task employed here and the standard discrimination situation say, in vision, in which frontal animals perform successfully, concerns the spatial relationships between the stimuli and the responses. The visual task involves discriminanda having definite spatial locations and these frequently conform to the spatial aspects of the responses. In

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the present auditory task the stimuli had only an indefinite locus which was moreover completely unrelated to the spatial aspects of the responses.

How, then, would frontal animals perform on the auditory analogue of the visual task? The standard discrimination situation might be approximated by the use of the Klüver pull-in technique. Pulling in either of two spatially separated food containers, each with its own speaker, would produce one of two auditory signals emanating from that container. Successful performance by frontal animals on such an auditory task would suggest, as one possibility, that frontal animals are impaired not in auditory discrimination learning, *per se*, but rather on tasks in which there are no close or well-defined spatial and temporal relationships between the stimuli and the responses.

Posterior temporal lesion.—Both in initial learning and in retention a slight deficit was evident in all 5 PT animals as compared with the 5 IT animals. While the result can only be considered as preliminary it is comparable to the early results which helped to establish a relationship between an extra-striate cortical area and visual functions, and therefore more intensive investigation is justified. A larger range of auditory problems and the effects of lesions of smaller areas within the posterior temporal region should be studied. Finally, the question as to the specificity of the deficit must receive further investigation. Clearly, greater significance would accrue to the slight but positive results of the present study if it could be demonstrated that animals with posterior temporal lesions showed no deficit in visual or somesthetic discrimination learning.

Comparatively little work has been reported on the effects of temporal lesions on aurally guided behaviour in monkeys. Such evidence as does exist suggests that damage limited to the primary auditory cortex is ineffective in producing "permanent" loss in auditory discriminations, but larger lesions encompassing auditory area I, II, and III (although these are variously defined) do result in permanent loss of at least some types of discriminations (Evarts, 1952; Jerison and Neff, 1953). Similar findings have been reported for cats (Diamond and Neff, 1957; Meyer and Woolsey, 1952), and dogs (Allen, 1945). In relating the present work to these earlier findings two comments must be made. Firstly, traditional research has generally been preoccupied with the search for cortical areas which are *critical* for audition. Findings of post-operative "amnesia," or retardation in re-learning, therefore, while common, have not received close examination. The interpretation has probably been made that while auditory habits can be abolished other equipotentials areas could assume auditory functions without a significant reduction in sensitivity. The studies of the effects of inferotemporal lesions on vision, however, suggest a different interpretation. What has been labelled "amnesia," in fact, might be associated with the imperfect retention normal animals often show (*see* fig. 2, top) plus a permanent impairment in the ability to acquire

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discriminations. Such impairment would be reflected in slower learning, not necessarily in *failure* to learn, and would become evident only with further post-operative testing, making full allowance for improvement which normal control animals show when given a series of new discriminations (Harlow, 1949).

Secondly, research on the effects of inferotemporal lesions on visually-guided behaviour strongly suggests that the impairment is a function of the difficulty of the task. Therefore, conclusions that cortical lesions disturb auditory "pattern" discriminations but no frequency discriminations are premature since the former tasks were almost certainly the more difficult ones (Diamond and Neff, 1957). Indeed, the fact that it is possible to interpret a different study as indicating that cortical lesions interfere with frequency but no intensity discriminations (Meyer and Woolsey, 1952), suggests that difficulty of task rather than any special dimension of the auditory stimulus is the significant parameter.

Summary

15 animals subjected to bilateral lesions in the inferotemporal region, the posterior temporal region, or the lateral frontal region were tested either for initial post-operative learning or for post-operative retention, of a simple auditory discrimination between white noise and a 1,000-cps. tone. It was found that inferotemporal animals were not impaired, posterior temporal animals were slightly impaired, and lateral frontal animals were severely impaired on this task. The results were the same for initial learning and for retention.

These findings are discussed with respect to the assertions that lesions in the inferotemporal region are modality specific in their effects; that there is a posterior temporal region which bears analogous relation to audition that the inferotemporal region does to vision; and that the effects of anterior dorsolateral frontal lesions on behaviour require re-evaluation.

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THE PROGNOSIS IN APHASIA IN RELATION TO CEREBRAL DOMINANCE AND HANDEDNESS

BY

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Prognosis of Post-apoplectic Aphasia

From the practical point of view, most aphasias consecutive to a cerebral stroke will be associated with paralysis or sensory disturbances in the limbs, hononymous hemianopia, etc., and the prognosis of all these disturbances will depend on the nature of the causal pathological process (thrombosis, embolism, hæmorrhage) as well as on a great variety of other factors such as general circulatory efficiency, local and general arteriosclerosis, efficiency of collateral circulation, all of which are important in the establishment of the prognosis. Diagnostic techniques allow us to estimate these factors with greater accuracy than a few years ago. The importance of thrombotic internal carotid occlusions and of carotid insufficiency requires no emphasis. We shall not deal, either, with the essential differences between the symptoms due to arterial and venous lesions. Functional disturbances, such as œdema of the ipsilateral cerebral hemisphere, which we have been able to verify in a personal case of carotid thrombosis by the transitory pineal shift, may be followed on recovery by a striking regression also of the language disturbances.

Aphasia due to vascular lesions, in which there is usually a mixture of receptive and expressive troubles, will tend to improve or not in parallel with the other neurological symptoms, and their prognosis will largely depend on the sudden or slow development of the lesions as well as on the patient's age and personality. I cannot analyse here the prognosis of aphasia according to its causes, its clinical types or to certain symptoms which I have already discussed in the report read before the Congress of International Association of Logopedics and Phoniatry (Subirana, 1956). In trying therein to be objective, I emphasized the extraordinary variability of the course of the disorder as the analysis of literature also shows. Clinical facts constantly disprove the belief that patients with expressive disorders have better chances of improvement than those with

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receptive disorders. Also the rule that post-traumatic cases offer better chances of recovery than patients who have had vascular strokes is often at fault and the symptoms do not always offer any safe basis for the prognosis. That is the reason why I submit here a prognostic criterion which is the result of my own observations.

Hand-preference and Hemisphere Dominance As Regards Language

(*a*) *Handedness.*—Since ancient times, people have been intrigued by the fact that without any apparent reason men choose one hand, usually the right, for all everyday activities requiring a certain skill and also prefer this hand for gesticulating. Having dealt with this opposite behaviour between right-sided and left-sided people (Subirana, 1952) I shall not discuss here the causes of such cerebral functional difference, and the reasons for which humanity has chosen the right hand after a period of probable manual equivalence. This possible original equivalence and bilaterality of the human species finds is recapitulated in the bilateral and unilateral stages that, according to Giesecke, Lesné and Peycelon, Lederer, Gesell, etc., follow each other in a child before he becomes right or left-sided.

The authors do not agree on the period of life in which this functional differentiation manifests itself clearly. Gaupp (1929), states that right-handed tendencies are already evident during the fourth month of life, while Gloning, Gloning, and Hoff (1954) believe that this differentiation does not become apparent till the age of five. Quadfasel (1955) discussing a communication by Roberts, says that hand preference can be observed at about 7 months and is more or less established at 2 years with partial ambidexterity up to the age of 6. These chronological variations can be due to several causes, and mainly to the mixture of innate and acquired factors discussed below.

If right-handedness were transmitted as a dominant Mendelian characteristic and left-handedness as a recessive one (Jordan, 1914–15), many facts would find their explanation. With Brain (1945) we think that a great number of factors, other than heredity, can play their part in the preference of one hand. The influence of relatives, teachers, etc., obliging the left-handed child to use the right hand disguises innate tendencies, and often these "shifted sinistrals" do not even suspect, when they have become adults, their original left-handedness.

In 1951 we studied the laterality factors of 316 normal children whose ages ranged from 6 to 14 years, and on whom we carried out 11 tests of manual skill and the tests of extensibility according to André Thomas' technique (a total of 12 tests), the results of which showed that the percentage of pure right-handedness was only slightly above 8 per cent. As to

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pure left-handedness, we could only find one case.[1] We remarked then that our number of pure right-handers was the same as the proportion of left-handers estimated by other authors. As to the rarity of pure left-handedness it must not surprise us. In fact, even Bloede's "official" left-hander, who writes with his left hand and does all everyday activities with this hand too, is nevertheless compelled to make many social concessions and consequently his left hemisphere has had usually more training than the right hemisphere of a right-handed man. Our bibliographical research has since then showed us that Koch (1933) Durost and Hildreth (1949) had already stated how extremely rare pure left-handedness is. But I cannot agree with Bauer and Wepman who think they can deny the existence of innate factors in the determination of conditions provoking aphasia in subjects that are perhaps unduly called left-handers or ambidextrous. According to these authors, left preferences are only due to acquired factors and they thus deny any value to the familial stock mentioned for the first time by Foster Kennedy (1916) and which we consider as having a great importance, as will be seen later on.

In our series we have found that the number of left-handed children diminished as they grow older.[2]

This brief review allows us to conclude (Subirana, 1952) that sinistrality and dextrality are not opposite human characteristics, and consequently we can apply to all statistics carried out in order to establish the Mendelian hereditary rules of handedness and to estimate the number of left-handers, the same criticism that Bethe already made in 1925. It is our opinion that between the pure left-hander (almost non-existent) and the pure right-hander (very rare), there is a continuous "chain" of subjects with various degrees of hand-preference. Our conclusions do not differ from those of Critchley (1954) when he stated that the term "left-handedness" may comprise at least the following:

(1) Pure left-handedness with genetically determined left-handed, left-eyed and left-footed preferences.

(2) Shifted sinistrality or genetically determined left-handedness complicated by artificial insistence on the use of the right hand for writing.

(3) Shifted dextrality, or genetically determined right-handedness, in

[1]As to the discussed relationship between the hand preferred and the leading eye, in 1951 we found that this disturbance of laterality was evident in 143 children out of our series of 316. In some of them the dominance has later on become unilateral but discordance still persists in a few and it is precisely among the latter that are found the children showing difficulties in reading and spelling, as has also been observed by Byron (1948). More recently Barger, Lavin and Speight (1957) insist upon the relationship between mixed laterality in children and their poor reading.

[2]Along with Oller-Daurella we have found in the EEG. of left-handed children a decrease of the percentage of the alpha-wave and an increase in the slow frequencies as well as greater anomalies during hyperpnea.

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which early affection of the right arm, right hand or left cerebral hemisphere has determined the shifting from dextrality to sinistrality.

(4) Left-handedness occurring in a predominantly right-handed family or right-handedness occurring in a predominantly left-handed family. The latter condition seems to have the greater significance, as a single sinistral in a family of dextrals may lead, fortunately for us, to unexpected sequelae in the case of a right-handed person with a brain lesion. Left-handedness seems to have a stronger influence than right-handedness.

(5) Complicated individuals who are at the same time left-handed and right-eyed and right-footed. In each one of these five sets of circumstances, the patient will be considered as being left-handed. Still, if a brain disease occurs in them, their reaction to disease will be completely different.

We also believe, together with many other authors, that the differences between sinistrality and dextrality cannot be expressed only be means of quantitative terms and that the left-handed man is not at all the mirror-image of the right-handed man. These differences will become even more evident when we see later the different response of right and left-handers to the experiments carried out by disease.

Let us now briefly review the relationship between handedness and hemispherical dominance as regards language functions.

(*b*) *Cerebral dominance and language functions.*—It is impossible to analyse here the large number of works published since 1836, when Dax mentioned for the first time how frequently right hemiplegia was associated with language disturbances. The theory that aphasia was a result of disease of the left-hemisphere was supported by the works of Bouillaud as far back as 1865, who spoke of "la gaucherie cérébrale" of Broca, Charcot, Hughlings Jackson, and Wernicke. In 1874 Jackson referred also to the "leading hemisphere" and reported with Ogle cases of left-handed patients whose aphasia was due to right cerebral lesions.

During the first years of this century neurologists tried to find an explanation of cases of lesion in Broca's area not associated with aphasia. Some of them, following Monakow's ideas of diaschisis, incriminated the substituting activity of the neighbouring cortex while most of them thought already of the opposite hemisphere. As to positive cases, only very few authors have been against the reciprocal part played by both hemispheres in the manifestation of aphasic symptoms as well as in the restoration of language functions.

The works of the anatomo-pathological school, backed up by Henschen's 1,500 observations, helped to establish the relationship between aphasia and left-brain disease in right-handed subjects. Henschen not only admits the substitutive function of the right hemisphere but also establishes the various degrees of this. These categorical assertions, however, do not strictly correspond to clinical facts.

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Among our contemporaries, Nielsen's ideas can be considered as the most representative of this school, although he has a much broader vision of the matter. For him the difference between two symmetrical functional areas in either hemisphere is only a matter of degree. All those who feel interested by the so-called hemisphere dominance should read his monograph: "Aphasia, Apraxia, Agnosia" in which are described the performances of the "major" and "minor" hemispheres.

The doctrine of cerebral dominance has been supported by many works dedicated to prove the relationship between handedness and congenital language disturbances. Subirana, Corominas and Oller-Daurelia (1950) studied congenital aphasia in children and the analysis of their cases led them to conclude, like Russell Brain (1945), that in these children the disturbances of hand preference is probably a concomitant symptom of aphasia and not its cause.

Several authors have wondered whether it is right to compare hemispherical dominance in handedness to dominance in language functions. The most striking difference between them lies in the fact that a right-handed man can voluntarily suppress all his right hand activities and substitute them more or less successfully with his left hand. He can certainly not do the same thing with his language functions.

Nielsen (1955) and Roberts (1951) agree on the impossibility of knowing, except when there is a lesion, which one of the two hemispheres functions as the major one for the language. The hemisphere, lesions of which had caused the aphasic disturbances, would be known, according to the dogma of general unilaterality of dominance, by means of the paralytic and sensory disturbances of the limbs, of homonymous lateral hemianopia, etc. As we shall see farther on, this criterion is not always valid. Von Hagen (1938) and many other authors think that it may be possible to modify any individual's inherited tendencies by training, so that a strongly left-brained person may be changed into a strongly right-brained individual provided the training is intensive and starts early enough in life.

Can we always rely on the global unilaterality of dominance? The classical cases of crossed aphasia that I studied (Paillas and Subirana, 1950) as well as the ever growing number of cases published in the literature by many authors of right hemiplegia with aphasia in left-handed people show us how complex this problem is and references to this will be made later.

Certain cases I have been able to study led me to admit, with Nielsen, that when the language function has been partly affected by a cerebral lesion it is not certain that it will be shifted "in toto" to the other hemisphere: the functions of temporal, parietal and occipital lobes would not always move together in their migration towards the healthy hemisphere. This so-called shifting would also occur quite differently in a predominantly left-handed subject, in a left-hander hiding under the

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aspect of a right-hander and in all the series of more or less pure right-handers. We could give a few examples of the preponderant influence of acquired factors on the organization of dominance which we could call specific for the various language functions. Let me only mention the personal case of a former syphilitic patient who suffered, at the age of 51, a left hemiplegia with aphasia and whose detailed description was given by Paillas and Subirana (1950). This previous case has not been included, however, in our present series.

This shifting of dominance could be brought about by two causes: by lesions directly affecting the use of the dominant limb and by lesions affecting the dominant hemisphere.

(1) *Lesions of the dominant limb.*—Oppenheim's well-known case commented on by Wernicke, of a right-handed girl who suffered an injury, at the age of 17, which made it impossible for her to use her right hand and who showed later a sensory aphasia and a left hemiplegia. The case of Lovell, Waggoner and Kahn (1932) is also very instructive. A male of 31 years of age who had a cyst in the language area of the right hemisphere, developed aphasia. The patient gave a history of pure right-handedness until the age of 10 when, because of an injury, the right hand was amputated at the wrist. Twenty-two years later a lesion of the "adopted" hemisphere resulted in aphasia.

(2) *Lesions of the dominant hemisphere.*—The critical review carried out by Needles (1942) proves to us, however, how complex this matter is. In fact, besides certain cases that support the idea of the possibility of a late shift of dominance he quotes some others that show how strongly this dominance remains sometimes attached to its former site. Basing himself on 522 patients upon whom operations were performed at the Montreal Neurological Institute for treatment of focal cerebral seizures, Roberts (1955) shows that some left and right-handers had aphasia after surgery on the left hemisphere despite previous extensive destruction of that hemisphere. For him, this shows that the assumption that following destruction of an area on the left, the right hemisphere takes over the functions of that area, has not been proved. Needles (1942) tried to find a logical explanation of all the apparently contradictory cases, feeling rather inclined to believe that in each one of them "a transitory aphasia would have appeared, even if the lesion had affected the language area opposite to the one it did affect." As Nielsen said, " Nature takes the course of least resistance." If it is easier for the slightly crippled left side to continue than it is for the untrained right side to take over, the left side will continue. We believe that at the present moment the best theory is that of transference of function to the other hemisphere.

The doctrine of cerebral dominance implies that the left hemisphere of dextrals will react to a lesion exactly as the right hemisphere of sinistrals. Let us briefly review this assertion in the light of the new contributions.

During the last century the preponderant importance of the left hemisphere had already been emphasized and it was admitted that most men were left-brained speakers, while they were right-handed. A minority of people, however, did not follow the general rule and their left-handedness led to a belief in the lateralization of their language functions in the right hemisphere. The cerebral pathology of the left side was considered to be the opposite in every way of the right-siders without taking into account that it is impossible to study the reaction caused by a cerebral lesion in right-handers who would have been compelled to write with their left hand.

Conrad (1949) made a critical review of the cases he had been able to study during the war, of left-handers who had shown aphasia following a cerebral wound. He divided his cases in three groups:

(1) The cases that corroborate the classical postulate in its two points:

(*a*) right-brained wound = aphasic disturbances

(*b*) left-brained wound = no disturbances.

He made no comments upon this first group.

(2) The cases whose symptomatology is reversed, that is:

(*a*) Language disturbances following a left-sided lesion. Everything would happen in them as though they were right-handers. Five cases are given.

(*b*) Absence of aphasic disturbances following a right-hemisphere lesion. Detailed description of five other cases.

(3) This third group includes the extreme cases in whom transitory aphasia occurred following injuries either on the left or the right side of the brain.

As this work by Conrad reveals unexpected aspects of this matter, some of them we feel should be mentioned here:

(1) The probability of presenting aphasic disturbances following a cerebral wound are greater in left-handers than in right-handers. However, in the former, prospects of recovery are better.

(2) Contrary to what might have been expected, most aphasic left-handers owed their condition to a left hemisphere lesion.

Conrad believes that these facts demonstrate that left-handedness is not simply a right cerebral predominance with physiopathological inversion as regards right-handedness, but that it is due to either a higher degree of bicerebrality (Beithirnigkeit) or a lower degree of hemispheric specialization.

The recent works published after Conrad's contributions and our own have helped us to fight the tendency to consider homologous, as far as aphasia is concerned, the functions of the left hemisphere in right-siders

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to those of the right hemisphere in left-siders. We can quote, for instance, the statements of Humphrey and Zangwill (1952*a* and *b*) with reference to the left-sider: "If left-brainedness were correlated with right-brainedness as has commonly been assumed, then aphasia would have been expected to occur only in the right hemisphere injuries". Although in their first survey these authors gave too great an importance to the left lesions in the production of aphasia in left-handers, when one sums up, as they have done recently, the many cases published in the literature, one sees that the left-hander is likely to present an aphasia, whether the lesion is located on one side or the other. The last work of Roberts agrees with this point of view. This author, using his personal cases and adding to them those collected in the literature, shows that 68 of 86 left-handed people had aphasia with disease of the left hemisphere and 60 out of 90 with involvement of the right hemisphere.

These figures given by Roberts and others, are based on aphasias due to destructive lesions. The interesting work of Hécaen and Piercy (1956) finds concordant results in analyses of cases of paroxysmal dysphasia and after a careful study in relation the site of the focus of the cerebral disturbance and the handedness of their patients, they conclude that there is good evidence to suggest more nearly equal bilateral representation of language in the two hemispheres in left-handed than in right-handed people.

One can argue against this bicerebrality of the left-handed people which we favour, that there have been cases published in which dysphasia occurred in association with a right hemisphere lesion in right-handed people. Nevertheless, if we analyse in these cases the existence of mixed preferences and familial stock, it seems that the figures obtained of the real right-handed with aphasia, consecutive to the lesion of the right hemisphere, are negligible.

Ettlinger, Jackson and Zangwill (1955) collect 15 published cases in ostensibly right-handed patients; 3 of these were classified as ambidextrous and in 9 there was familial evidence of left-handedness. A great number of authors agree on the transitory character of aphasias in left-handed people. We shall come back to this point when we analyse personal cases.

It would be very interesting to study now the role played by the minor or the subordinate hemisphere, when it is the left one in left-handed people. That would oblige us to review the non specific symptomatology of the lesions depending on either hemisphere, and the specific ones consecutive to the involvement of one or other side of the brain. We would never be able to do so as accurately as Critchley (1953) says: "When the parietal lobe is affected in a left-hander we observe dual phenomena, that is, troubles belonging to the series of those derived from lesions from the major hemisphere mixed with troubles belonging to the symptomatology of the minor hemisphere".

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Analysis of Personal Cases

Out of 250 patients who showed signs of a cerebral vascular syndrome, 161 had unilateral hemisphere lesions: having given the details of all these cases and split up in tables corresponding to the left hemisphere lesions (106), and right hemisphere lesions (55) in a previous paper, we now limit ourselves to 161 cases of unilateral lesions arranged according to the sidedness of the patient.

Table I.—161 Cases of Unilateral Hemisphere Lesion

	Right-handers	*Left-handers*
Total number	153	8
Cases of aphasia ..	102	6
Rate of aphasia	66%	75%

This table shows that the global number of right-handers who had an aphasia consecutive to unilateral lesion is higher than those of left-handers but we can also find that, as we believed in 1951, the relative percentage of left-handers who suffer an aphasic disturbance following unilateral lesion is rather higher than in right-handers.

Let us now see how different these ostensibly right-handers will appear when they are submitted to the analysis of signs revealing their personal or family left-sided tendencies.

Table II.—102 Cases of Aphasia in Right-handers

	Signs of left-sidedness	*Without signs of left-sidedness*
67 cases of right hemiplegia and aphasia following a parallel course	14	53
9 cases of persistent aphasia with no right hemiplegia	1 (?)	8
23 cases of transitory aphasia and persistent right hemiplegia	19	4
3 cases of left hemiplegia and transitory aphasia	3	0

If we join the first groups we have 76 patients whose aphasia had no isolated regressive character and we see that only 15 of them showed signs of left tendencies (19·8 per cent). On the contrary, in the two other groups with 26 cases of isolated regression of the aphasia, the number of cases with signs of left tendencies is of 22 (84·5 per cent).

Table III.—6 Cases of Aphasia in Left-handers

3 cases of right hemiplegia with transitory aphasia.
2 cases of left hemiplegia with transitory aphasia.
1 case of aphasia with no left hemiplegia (and right hemisphere electroencephalographic focus).

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Just as I did a few years ago, I still agree with Conrad on the transitory aspect of aphasias in left-handers. I am well aware of the fact that the number of our left-handers is limited and I am not forgetting the cases in the literature, mainly the two cases of Dejerine who were left-handers and presented left hemiplegia; in one of them the aphasic syndrome disappeared later, while it persisted in the other. Dejerine thought this different course was due to acquired factors. The case of persistent aphasia was a complete illiterate and this fact raises another interesting question.

After what I have said I might classify my cases in four groups:

(1) The right-handers in whom no left lateral tendencies or left-sidedness in family stock can be discovered: *Group R.*

(2) The so-called right-handers in whom we find either these tendencies or this familial stock: *Group r.*

(3) The obvious left-handers who have, however, made more or less important concessions to the world of right-handers: *Group l.*

(4) The irreversible left-handers: *Group L.*

The respective course of the aphasia in these different groups is illustrated in the next table which sums up our present views upon the prognosis of aphasia.

TABLE IV

	Total number of cases	*Cases with transitory aphasia*	*Percentage with transitory aphasia*
R	65	4	6%
r	37	22	59·5%
l	6	6	100%

As can be seen, I have suppressed in this last table Group L, as none of the cases of aphasia in left-handers I have examined have deserved the "L" classification. Do the rare cases of persistent aphasia in left-handers mentioned in literature belong to this group?

This last table shows in a very striking manner that the percentage of patients in whom the aphasia is transitory in spite of the persistence of the hemiplegia is almost ten times higher in group "r" than in group "R". As to group "l" the percentage of recovery is of 100 per cent according to our experience.

Although I do not pretend it is the most important factor of all, I think that the study of non-apparent individual preferential sidedness or of left-sided family stock provides us with most valuable information in the prognosis of aphasia. The more an individual is basically right-handed the less we shall expect to see the regression of his aphasia.

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THE PHYSIOLOGICAL BASIS OF CONSCIOUSNESS

A Critical Review

BY

RUSSELL BRAIN

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I.—Introduction

There are perhaps no more complex problems in neurology than those which arise in connexion with consciousness, and few topics more plentifully breed confusion. Much work in relation to it has been done by experimental physiologists. This raises two problems. Modern electrophysiological methods are highly technical, and in certain respects remote from the experience of clinical neurologists. Their interpretation is both difficult in itself and hard to correlate with clinical observations. Moreover, consciousness in animals is an inference from behaviour far more indirect than in the case of man, who can describe his own conscious states. Both human and animal observations raise a further problem of interpretation. Whether we apply an electrical current to the brain or observe the symptoms of an epileptic attack or of a destructive cerebral lesion, it is often difficult to decide how what happens is related to normal function. In the first two instances it may be said that the stimulus is not physiological, and that we do not know if its effect is limited or diffuse, excitatory or paralytic. Indeed the matter is more complex than that, for the nervous pathway excited by an excitatory stimulus may itself be either excitatory or inhibitory in function.

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Finally, assuming these difficulties to be overcome, we cannot escape a question which is inherent in the interpretation of our observations, namely the meaning of "localization" and "representation" when applied to the nervous system in connexion with consciousness, which is only a special instance of the more general problem of the relationship between nervous structure and function.

It seems to me that the time has come to attempt to clarify these interrelated questions. Although some of them are very old, the numerous new facts discovered both by neurophysiologists and clinical observers call for a review of the physiological basis of consciousness.

(i) *The Meanings of "Consciousness"*

An initial confusion arises out of the meaning of the word "consciousness." Let me illustrate this from some of the statements about consciousness made by contributors to the Symposium "Brain Mechanisms and Consciousness." "The organism's state of general excitability—which includes alertness and consciousness" (Hess, 1954); "To quote Stanley Cobb . . . 'It is integration itself, the relationship of one functioning part to another, which is mind and which causes the phenomenon of consciousness.' This phenomenon we propose to call an 'experienced integration' or EI, in order to distinguish it from mental integrations in general, for most of these remain unconscious (unexperienced)" (Fessard, 1954); "I consider integration as a dynamic abstraction and not localizable in space" (Bremer, 1954); "Momentary distributions of patterns of subthreshold excitatory and inhibitory states in limited neural spaces, rather than the total aspect of propagating impulses through neural nets, has [*sic*] been proposed here as the basis for conscious experience; but what makes a pattern 'conscious' of its own patterning remains an irritating problem" (Fessard, 1954); "A relation exists between cortical electrogenesis and the state of consciousness" (Gastaut, 1954); "The existence of something called consciousness is a venerable *hypothesis*: not a datum, not directly observable, but an inference from other facts. . . . Assume then that consciousness is something within the head which determines behaviour" (Hebb, 1954); "There is no one criterion of consciousness" (Lashley, 1954); "My own data make it clear that consciousness of anything implies and depends on an ability to differentiate an 'I' from a 'non-I' world" (Kubie, 1954); "The subject-object relation . . . is based upon a false analogy with the relation of the body, as agent, to the environment. . . . The knower as an entity is an unnecessary postulate" (Lashley, 1954); "Although we cannot get along without the concept of consciousness, actually there is no such thing" (Kubie, 1954). It is clear from these quotations that the term "consciousness" is being used in different ways. The question: "What is consciousness?" can mean at least six things:

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(1) What are the forms of behaviour by which we distinguish between the conscious and the unconscious individual?
(2) What psychological terms can be used to describe conscious states such as sensory and perceptual experiences?
(3) How is consciousness to be understood in relation to the activity of the nervous system?
(4) What is the role of consciousness as a biological function of the living organism?
(5) What logical terms are the right ones to apply to conscious experience? or
(6) What is the metaphysical status of consciousness?

The fact that these questions are interrelated makes it easy for confusion to arise in discussions unless care is taken to avoid using the term "consciousness" in different ways without drawing attention to the fact.

The peculiar difficulties which confront the neurological investigation of consciousness, raise at the outset a question of procedure. Are we to begin by considering observations which have been made on animals, or with disorders of consciousness in man? Against beginning with animals it may be urged that the consciousness of animals is a remote inference from their behaviour, and, even if present, must be of a very much simpler nature than human consciousness: can we expect that observations on animals will throw much light upon consciousness in man? Yet in my view it is essential to begin with animal experiments. Numerous observations can be made on animals which cannot be made on man. For this reason human neurophysiology owes most of its fundamental facts and principles to animal experiment. Secondly, it is a sound and generally accepted principle to start with normal physiology, and seek to understand the effects of disease as disorders of the normal, though it is true that disease often leads to an enlargement of our knowledge of the normal. The only normal form of altered consciousness is sleep, and it is safe to say that there is far less difference between the sleep of man and of animals than there is between their waking states. Anything we can learn therefore about the physiology of sleep and awakening in animals should be of value for our understanding of the physiology of consciousness in man. We shall begin then by considering the results of animal experiment, bearing in mind that since animal experiment often proceeds by the production of lesions of the nervous system, normal physiology is often an inference from disordered function, but that is true of physiology in general.

II.—The Central Reticular Formation

Since the central reticular formation figures so largely in the literature of the physiological basis of consciousness, it is necessary to begin by

giving some account of it and of the way the term is used by various writers. As Olszewski (1954) points out, "Anatomically, the name reticular formation has been applied to those parts of the lower brain-stem which in the myelin stain are characterized by an interlacing network of fibre bundles." It is therefore anatomically poorly defined, and its anatomical definition is unrelated to its functions. These are many, and include others besides those related to consciousness. "The anatomical and physiological conceptions of the reticular formations do not correspond with each other" (Olszewski). Defining the area under consideration in another way, Olszewski says: "It includes all the grey masses of the tegmentum of the medulla, pons and mid-brain, which do not belong either to the normal nerve nuclei, to the relay nuclei of the cerebellar system or to the relay nuclei of the lemniscal systems." When, as we shall see, experimental studies of this part of the brain led to the conclusion that it played an important part in maintaining consciousness, what was originally a rather crude anatomical description was given a physiological meaning, exemplified by the term "ascending reticular system," which appears to mean that part of the central reticular formation which contains centripetal pathways involved in the regulation of consciousness. As these functions of "the reticular formation" were traced up into the thalamus, the "thalamic reticular system" became incorporated in it. The difficulties of nomenclature have arisen primarily because details of the nuclei and paths in the reticular formation concerned with consciousness are still unknown, and the term "central reticular formation" has been found a convenient comprehensive term for them. For the present, no doubt, it will continue to be used in this sense, but it must be remembered that the reticular formation is neither an anatomical unit nor a physiological entity, and that even in its relationship to consciousness its functions and relationships are complex and varied.

III.—The "Reticular Alerting System"

(i) *Experimental Evidence*

In the early days of electroencephalography, Rheinberger and Jasper (1937) studied the electrical changes in cats in relation to sleep and wakening, and "activation" associated with "desynchronization" of the electrical rhythms occurring in the cortex in response to afferent stimuli. It was many years before much more was learned about the activating process. The considerable recent additions to our knowledge are summarized by Magoun (1954). His "work began with the chance observation that direct electrical excitation of the reticular formation of the brain-stem induced changes in the EEG seemingly identical with those observed in awakening from sleep, or alerting to attention, and which have been referred to variously as activation, desynchronization,

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EEG arousal or the blocking reaction. . . . The regions of the brain-stem from which such EEG arousal could be induced included the reticular formation and tegmentum of the lower brain-stem and, in the diencephalon, the subthalamus together with the dorsal hypothalamus and ventromedial thalamus. . . . Since the EEG changes evoked by stimulating this reticular system resembled so closely those of arousing peripheral stimuli, it became of interest to determine whether afferent paths made connexions with the reticular mechanism in the brain-stem." French, von Amerongen and Magoun (1952) studied the EEG changes resulting from alterations in the electrical activity of the brain-stem and the cortex which occurred in monkeys as the result of various forms of sensory stimulation. They demonstrated that sensory stimuli excited not only the well-established laterally-placed ascending pathways but also a medially-situated system in the brain-stem, excitation of which caused cortical desynchronization characteristic of the change in the EEG from drowsing to wakefulness. French, Verzeano and Magoun (1953*a*) further analysed the properties of these two ascending pathways, and found that electrical potentials in the lemniscal pathways showed rapid conduction, segregation according to sensory modalities, and discrete cortical projection to the primary receiving areas. The medially-conducted potentials, on the other hand, showed slower conduction, common transport for all modalities, indicated by the mutual influence of suitably timed stimuli of different sensory qualities, and distribution to wide areas of cortex by diffuse projection from the medial centrum and the intra-laminar nuclei of the thalamus.

Since these points are fundamental to an understanding of the function of the central reticular formation in relation to consciousness, it is necessary to report them in a little detail. French, Verzeano and Magoun (1953*a*), state that on a stimulation of the sciatic nerve impulses reached the medial lemniscus at the level of the mid-brain in 6–9 msec. and the post-central gyrus in 10–12 msec. When auditory stimuli were used, impulses reached the lateral lemniscus and auditory cortex in 13–17 msec. The same stimuli also evoked impulses which reached the mesencephalic tegmentum and mid-line thalamic nuclei in 13–23 msec. and took correspondingly longer to reach the frontal associational cortex. The authors suggest that the lateral lemniscal pathways are concerned with the conduction of sensory impulses which contribute to the perception, recognition, localization and quantitative discrimination of stimuli, while the medial pathways are concerned with the initiation and maintenance of the conscious state, providing in this way the necessary background of activity without which no integrative sensorimotor or adaptive behaviour is possible. We may note in passing a point on which no comment seems hitherto to have been made, and to which we shall return later. The experiments just quoted show that the ascending

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reticulo-cortical impulses, which are credited with initiating and maintaining the conscious state, arrive at the cortex *after* the impulse excited by the same stimulus which is held to be responsible for those perceptual elements which comprise the content of consciousness. A number of workers, among them French and Magoun (1952), have studied the effects of experimental lesions in the central cephalic portion of the brain-stem. These authors found that complete destruction of this area was not compatible with survival, while less extensive lesions resulted in akinesis and hypersomnia, a condition resembling coma in man. The EEGs were characterized by hypersynchrony, which did not respond to the stimuli normally causing sensory arousal.

Magoun (1952) describes the different effects of interrupting the two types of ascending pathway in cats. A cat with mesencephalic interruption of the lemniscal pathways remains as wakeful as a normal animal and its EEG exhibits typical activation. When such an animal is asleep it can still be awakened by auditory and somatic stimuli which, it is concluded, can only operate upon it through the central reticular formation, since the ascending sensory pathways have been divided. The cat with destruction of the central reticular formation, on the other hand, behaves "as though deeply asleep or anæsthetized, and its EEG exhibits the large slow waves and spindle bursts of sleep."

(ii) *The Action of Anæsthetics*

The mode of action of barbiturate anæsthetics is reviewed by Brazier (1954). The cortical response to sensory stimulation under barbiturate anæsthesia was studied by Forbes and Morison (1939) who distinguished a primary response restricted to the appropriate specific sensory projection area and a secondary discharge which was a diffuse response of the whole cortex. They suggested that these two responses depended upon dual ascending systems. Dempsey, Morison and Morison (1941) concluded that on stimulation of a sciatic nerve the primary response of short latency travelled by the medial lemniscus to the contralateral leg area of the sensorimotor cortex, while the secondary response of long latency travelled by both crossed and uncrossed pathways. The site of origin of the secondary response and its relation to the recruiting response of the intralaminar nuclei and the observations of Jasper and Droogleever-Fortuyn (1947) are discussed by Brazier, and need not be considered in detail at this point. The features of barbiturate anæsthesia which are important for our present purpose are that "a state of anæsthesia does not require that sensory impulses should be prevented from reaching the cortex," i.e. that in the anæsthetized animal the primary response continues to occur; and, secondly, that "barbiturates appear to have a differential depressant action on a subcortical inhibitory system, the result being an augmentation of response in the non-specific

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sensory system that carries Forbes' secondary response." Brazier concludes that "a disruption of balance between inhibition and activation at a subcortical level of integration would appear to determine whether incoming sensory impulses receive the elaboration necessary for awareness." French, Verzeano and Magoun (1953*b*) present evidence that anæsthetics block the central reticular formation at a time when conduction in the lemniscal pathways is unaffected. They believe that this is the main factor in anæsthesia though some blocking of the lemniscal systems may occur, and some change in the interneuronal cortical systems.

The researches of Gellhorn (1954) and his collaborators have reached similar conclusions. They observed (Murphy and Gellhorn, 1945), that stimulation of the hypothalamus causes generalized excitation of the cerebral cortex, while nociceptive stimuli, having a similar effect on the cortex, produce signs of excitation of the hypothalamus (Gellhorn and Ballin, 1946). In deep anæsthesia nociceptive stimulation produced a generalized cortical excitation, whereas proprioceptive and acoustic stimuli failed to do so (Bernhaut, Gellhorn and Rasmussen, 1953). Gellhorn (1953*a* and *b*) studied the effect of low and high concentrations of CO_2 on the hypothalamic-cortical discharges. He found that low concentrations of CO_2 increased psychomotor activity and augmented hypothalamic-cortical discharges. High CO_2 concentrations have the opposite effect. Gellhorn (1953*c*) also found that in barbiturate anæsthesia, the generalized reactions to nociceptive stimuli are abolished whereas the excitation of specific cortical projection areas in response to acoustic and optic stimuli persists.

(iii) *The Reticular Formation and Sleep*

Magoun (1954) summarizes "present conceptions of the functional organization of the activating system of the brain-stem" as follows. "Its direct stimulation desynchronizes the EEG in a manner simulating awakening from sleep or alerting to attention. Collaterals from all afferent paths to the cortex turn into this subcortical system and EEG arousal induced by afferent stimulation can be shown to be mediated through it. Injury to its cephalic portion leads to chronic loss of wakefulness. Reversible pharmacologic block of its ascending influences upon the hemisphere may provide a neural basis for the anæsthetic state." It should be noted that although in this passage Magoun speaks in one place of "wakefulness" which is a description of an animal's behaviour, he speaks also more cautiously of desynchronizing the EEG "in a manner simulating awakening from sleep or alerting," and also of "EEG arousal."

Bremer's (1935, 1936) earlier studies of the *cerveau isolé* in relation to sleep led him to take the view that when the brain of an animal was

transected at the level of the upper brain-stem, the cortex exhibited the EEG changes of sleep. He attributed this and the failure to arouse the animal to the fact that its ascending sensory pathways had been divided. The work of Magoun and his associates has necessitated a modification of this view. Bremer (1954) accepts "the conception of the meso-diencephalic sleep-regulating apparatus as a mechanism of vigilance," but he stresses the need for a broader view of its action and interactions. The problem is why in the *cerveau isolé* the rostral portion of the reticular grey matter is not sufficient to maintain wakefulness. He concludes that "the caudal part of the reticular formation which (in the *cerveau isolé*) is disconnected from the telencephalon and diencephalon, possesses, by reason of the richness and variety of its afferent connexions, the greatest functional importance. In this multi-synaptic neuronal system, the tonic activity of the proximal parts apparently depends upon that of the distal segment." But in Bremer's view, an exclusively reticular theory of sleep regulation is inadequate. In particular it does not take account of impulses descending from the cortex. The reticular formation reacts to cortical stimulation, and brief faradization of a few seconds duration of non-convulsive intensity at widely distant areas of the cortex awakens the sleeping animal. Moreover in the *encéphale isolé* when the auditory cortical areas are intact, EEG arousal can be evoked by a voice call, but this does not occur after destruction of the auditory areas, though a tactile stimulus is still effective. Bremer takes a holistic view of the process of falling asleep. He finds no need for a specific hypnogenic mechanism or centre as postulated by Hess (1954) on the basis of stimulation experiments which are open to disputed interpretations. According to Bremer "a slackening of activity of any region of the brain must result in a lowering of excitatory state in areas or nuclei—including the reticular formation—with which the region in question has facilitating relationships, and so the whole of the synergic structures are gradually affected. Doubtless, 'the functional depression' of the reticular formation, on account of the latter's central position in the homeostatic mechanism of arousal, plays a preponderant, if not always an initial, role in this process of cumulative 'defacilitation'."

The term "sleep" has been applied to other fragments of the nervous system besides the *cerveau isolé*. It is an old observation that states of relaxation akin to sleep occur in the decerebrate preparation. Rioch (1954) distinguishes between a preparation transected at the rostral end of the mid-brain and one transected at the caudal end. The former exhibits some of the phenomena of sleep; the latter does not. Bard and Macht (1958), however, recognize "a behavioural change that resembles sleep" in both "high mesencephalic" and in "pontile" cats, i.e. in those transected at the rostral and caudal limits of the mesencephalon respectively.

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IV.—Attention and Perception

(i) *The Influence of the Cortex on Afferent Impulses*

The work of Magoun and his collaborators has directed attention chiefly to the ascending pathways which are believed to facilitate the response of the organism to the arrival of sensory impulses, and in general to arouse it and maintain it in a state of "alertness." Bremer's work, just quoted, draws attention to the importance of corticofugal impulses in this connexion and we must now consider the evidence which is accumulating that such descending impulses are part of the response to sensory stimulation. Dawson (1958) has observed that in certain patients suffering from myoclonic epilepsy "a sensory stimulus applied to the periphery leads to an electrical response, recordable from the scalp over the sensory area, which is many times larger than that found in healthy people" (Dawson, 1947*a*, 1947*b*). A similar condition can be created artificially by giving chloralose or trichlorethylene to rats, and in such animals Dawson has shown that at some levels of anæsthesia, the afferent volley produced by sensory stimulation may be considerably modified even at the first sensory synapse, i.e. in the cuneate nucleus. Scherrer and Hernández-Peón (1955) working with unanæsthetized curarized animals, have shown that a comparable modification leading to depression or even abolition of this post-synaptic impulse—which they call "a true inhibitory effect"—could be produced by stimulation of the sensory cortex or the reticular formation.

Hernández-Peón and Hagbarth (1955) have shown that repetitive cortical and reticular stimuli cause depression of afferent test volleys in the trigeminal sensory nucleus, while Kerr and Hagbarth (1955) have studied the centrifugal fibre system entering the olfactory bulb from the brain and have shown that olfactory impulses can be depressed by stimulating the basal rhinencephalic area and the anterior commissure.

Anatomical studies have suggested pathways by which this influence of the cortex on sensory impulses can be exerted. Walberg (1957) has shown that ablation of various parts of the sensory cortex produces degeneration of fibres terminating in the cuneate nucleus on either side, and Brodal *et al.* (1956) have demonstrated degeneration of fibres in the trigeminal sensory nucleus after cortical ablations. These authors conclude that the afferent inflow is normally controlled by a tonic activity descending from the cortex, cerebellum or brain-stem, and they found that this system is very sensitive to anæsthesia. Hernández-Peón and Hagbarth (1955) have investigated the mutual blocking action of paired stimuli in the reticular system, and Bremer (1954) has shown that the electrical response to a click in the reticular formation is diminished when it is preceded by the electrical response there to cortical stimulation. Hernández-Peón *et al.* (1957) have examined the effect of competitive

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stimuli upon the electrical responses in the cortex, and found, for example, that the responses to a flashing light recorded from the occipital cortex of the cat were almost abolished when the animal was given fish to smell. There was evidence that the reduction in cortical activity was due in part at least to a reduction in the afferent inflow.

(ii) *The Cortex and Attention*

Adrian (1954) discusses the role of the cortex in perception and the physiological mechanism of attention. "The operations of the brain," he writes, "seem to be related to particular fields of sensory information which vary from moment to moment with the shift of our attention. The signals from the sense organs must be treated differently when we attend to them and when we do not and if we could understand where and how the divergence arises we should be nearer to understanding how the level of consciousness is reached. . . . We have . . . two possibilities which might be put forward. One is that the afferent signals from e.g. the ear may be summarized on their way up the auditory pathway, but that the content of their message is allowed to reach the cortex whatever may be going on in the other sensory pathways. . . . The other possibility is that the controlling mechanism operates at an earlier stage and that we attend to the sound and are unaware of contacts and pressures because the auditory signals are allowed to reach the cortex and the tactile signals are not." As he points out, the fundamental difficulty is that we do not know what is the relationship between cortical electrical changes and what is going on in consciousness, in particular we do not know "whether the appearance of a wave rhythm in the cortex does or does not involve increased activity in the cortical neurones." These difficulties remain for the present, but some new facts have emerged since Adrian's paper which perhaps enable us to form at any rate a clearer hypothesis of what may be going on as the physiological basis of attention. In discussing this it is necessary from time to time to leap the gulf between brain and consciousness, as Adrian himself does in speaking of our "attending to the sound" and being "unaware of contacts and pressures." We need not apologize for this, for though we can in a metaphorical sense speak of an animal's attending to a sound, attention connotes a state of mind of which we have direct experience only in ourselves. It is in studying attention that, as Adrian says, we approach most closely to the level of consciousness, for in relation to attention the same percept slips in and out of consciousness. "The climax of mental integration," says Sherrington (1940), "would seem to be attention."

What then, in summary, are the physiological facts of which any explanation of attention must take account.

(1) The production of an electrical change at the primary sensory cortical area in response to sensory stimulation is not necessarily

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accompanied by consciousness, since such a change may occur, and even be enhanced, when the subject is anæsthetized.

(2) Stimuli to one sensory channel may diminish the electrical cortical responses to simultaneous stimulation by another.

(3) This is due in part at least to the influence of the prepotent sensory stimulus upon the conduction of impulses in the corticipetal pathways, whose activity is diminished.

(4) Descending pathways have been shown to exist from the cortex to nuclei in the course of the afferent sensory pathways, and stimulation of these descending pathways at various levels, including the cortex, and the reticular formation, diminishes the post-synaptic activity of the afferent pathways upon which they discharge.

(5) Collateral afferent pathways which go to the reticular formation from the main lemniscal pathways show mutual interference of impulses derived from different sensory modalities.

(6) Cortical stimulation excites electrical changes in the reticular formation which diminish its responses to sensory stimulation.

It would at any rate explain the facts if the arrival of sensory impulses at a specific cortical area were capable of exciting corticofugal impulses which have an inhibitory effect upon the afferent pathways of other sensory modalities.

(iii) *The Reticular Formation and Attention*

We must now turn back to the diencephalon. As we have seen, the reticular formation is aroused by collateral impulses from the main sensory pathways and by descending fibres from the cortex, and Scherrer and Hernández-Peón (1955) have shown that stimulation of the reticular formation can depress the post-synaptic sensory impulse. It is probable, therefore, that the reticular formation plays a part in the control of attention, the details of which have yet to be ascertained. Some light has been thrown upon this by the recent experiments of Sharpless and Jasper (1956) on the physiological mechanism underlying habituation of the arousal reaction, i.e. the tendency for a repeated stimulus to lose its arousing effect. Working with sounds, these authors distinguished two types of arousal reaction, one of short latency and brief duration and the other of longer latency and greater persistence, which they called the phasic and the tonic reactions respectively. Their experiments showed that habituation does not depend upon changes occurring in the specific auditory system, and survives complete destruction of the auditory cortical areas. They conclude that "the tonic and persistent arousal response is probably mediated by the lower portions of the ascending reticular system and the more rapid and more highly differentiated response by the upper portions of the activating system, particularly the unspecific thalamic projection system and adjacent sensory structures."

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What is the significance of the fact, to which I drew attention earlier, that electrical impulses excited by sensory stimuli reach the cortex later when they pass through the reticular formation than when they arrive by way of the lemniscal pathways? It follows from this that if the reticular formation is to be regarded as "an alerting system," this cannot mean that in some way it prepares the cortex in advance for the reception of a sensory impulse: it looks rather as though its function were to prepare not only the cortex but the other sensory pathways also to respond to a sensory impulse when it has arrived. As we have seen, such responses are at least twofold, namely the reduction of other sensory "information" which might compete for attention, and the integration of the sensory "information" being attended to with the continuously changing background of somatic and environmental sensory data. This is borne out by recent evidence that the reticular formation plays a similar part in the establishment of conditioned reflexes (Gastaut, 1958).

(iv) *The Physiological Background of Perception*

What we have been considering so far is an over-simplified account of the physiology of attention, for living organisms do not attend or respond only to isolated stimuli, but also to percepts over a wide range of complexity. Adrian (1954), speaking of his experiments on the rabbit's olfactory experiences, says: "It looks as though the quality of the smell may be signalled by the arrival of impulses in particular fibres which are scattered over most of the receiving area, although they may be more numerous in one part of the area than another. It may be then that smells are distinguished by the fine detail of the receptor pattern as well as by its over-all distribution." Even for the rabbit perceptual discrimination is a necessary preliminary to the selection of the appropriate action. But if a percept is more than an isolated stimulus it is also normally more than an experience limited to one sense. Even the rabbit's smell relates to "something, somewhere," i.e. it has spatial reference. I am at this moment attending to the writing-pad upon which I am writing, but this pad has a certain position in space of which I am aware in relation to that of my own body, and I vaguely perceive other objects similarly orientated which form a background to the writing-pad. A single percept is thus also an abstraction. It is the focus of attention in a much wider field, the other ingredients of which may not at the moment be equally interesting but are just as essential, even though most people, including most philosophers, are unaware of the rich and complex contributions which the bodily proprioceptors make to the "simple experience" of seeing an object. This is true also of awareness of a part of the body, as I have pointed out elsewhere (Brain, 1950), and as is implied in Head and Holmes' (1920) concept of the postural schema.

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It follows that while the arrival of a nervous impulse at the appropriate sensory cortical area may be a necessary condition of a conscious experience it cannot by itself be a sufficient condition, for consciousness presupposes the contemporary activity of large areas, perhaps the whole of the cerebral cortex. What attention does is to use the discriminative power of the cortex to focus consciousness upon a certain perceptual experience at any particular moment. This is a complex process in which the cortex, the reticular formation and the sensory inflow all appear to be involved. Jasper (1954*a*) has suggested that alerting processes involving highly complex perceptual discrimination probably depend upon "some form of interaction between elaborate patterns in specific thalamic-cortical systems and brain-stem or thalamic reticular systems."

What determines the distribution of attention? I spoke above of "a prepotent stimulus." In animals in the wild state this is a biological concept, depending primarily upon the inherited organization of the nervous system. Bernhaut, Gellhorn and Rasmussen (1953) have demonstrated the prepotency of nociceptive stimuli in the arousal reaction. The endocrine system influences nervous reactions especially in relation to reproduction. The nest-building instincts of birds have been shown to depend upon a complex series of activities, of which the completion of one releases the next. In man the direction of attention is determined sometimes by simple, sometimes by the most complex psychological factors.

V.—The Physiology of Sleep

Current views on the nature of sleep are expressed by Magoun (1954), Hess (1954), and Bremer (1954). The facts discovered about the central reticular formation are valuable, but they must not lead us into an oversimplification. It has too readily been assumed, on the basis mainly of cortical electro-encephalography, that the effect of destroying the central reticular formation can be equated with sleep. It is true that the EEG in animals subjected to such lesions shows synchronized waves which resemble those found in sleeping animals. But such waves may merely indicate widespread cortical inactivity; "sleep" induced either by destruction of the reticular formation or by transection of the brain-stem is, even allowing for limited "arousal" reactions, sleep from which there is no awakening. It therefore lacks one of the cardinal features of sleep, and might better be described as coma, in which case it leaves us with the problem of the relation between coma and sleep. We have just seen how intimately cortex and reticular formation are related in attention, and there is evidence of their equally close relationship in sleep, which can be regarded as a generalized withdrawal of attention. Bremer (1954) and others (Livingston, 1954; Jasper, 1954*b*) have shown

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that cortical stimulation can "arouse" the transected cerebral preparation. Adrian (1937) wrote: "The unfamiliar noise wakes the sleeper because the afferent message reaches the cortex and is there judged as important. The cortex signals back to the diencephalon and the rapid spread of activity ensues. The facilitation is therefore between cortex and thalamus as well as between neurone and neurone." Equally the familiar noise, a baby's cry, may awaken a mother who can sleep through a thunderstorm. The "judgment of its importance" must surely depend upon cortical function. We must conclude that the cortex facilitates the reticular formation as well as the reticular formation the cortex. The restriction of sensory stimuli by closing the eyes, relaxing the muscles, etc., which we adopt in order to induce sleep may well have a central effect of depressing the reticular activating system which in turn depresses cortical activity. In view of the cortical depression of competing sensory stimuli involved in attention, it is tempting to think that the same process generalized by the reticular formation may play a part in sleep by depressing all sensory afferents. And we must not forget the inhibitory effect of the reticular formation upon muscle tone (Magoun and Rhines, 1947), which in turn would reduce afferent impulses from the muscles and joints. Muscular hypotonia may thus be less the result of sleep than one of its causes. In Bremer's words, "The physiological process of falling asleep may be explained, without necessary recourse to the hypothesis of a hypnogenic centre, by the cumulative de-activation (de-facilitation) of the encephalic neuronal networks resulting from synaptic fatigue and favoured by a reduction in the exteroceptive and proprioceptive sensory afflux. In this process of neuronal de-activation which culminates in sleep, the functional slackening of the brain-stem reticular formation, by reason of the latter's central situation in the nervous apparatus of arousal, plays without doubt an essential role." Both cortex and reticular formation equally play a part in awakening, and in order that awakening may occur we must suppose that a sufficiently strong stimulus puts into reverse the "chain-reactions" upon which sleeping depends. The ability to differentiate between stimuli and awaken in response to one but not another has been thought to be a cortical property, but recent work on conditioned reflexes indicates that the reticular formation possesses considerable selectivity in dealing with afferent impulses (Gastaut, 1958).

(i) *Is There a "Sleep Centre"?*

Hess (1954) in a paper entitled "The Diencephalic Sleep Centre" maintains that "the organism's state of general excitability . . . is regulated by two antagonistic centres," one of which produces alertness, and the other sleep. From what has just been said it will be clear that the normal processes of falling asleep and awakening can neither be regarded

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as initiated in nor controlled by a "centre." What Hess's experiments show is that electrical stimulation of a circumscribed area of the diencephalon in the cat produces "a sleep-like state." Even if this be true sleep the experiment proves no more than that there exists not a "sleep centre" but a "hypnogenic centre," to use Bremer's phrase, i.e. an area the electrical stimulation of which causes sleep. Hess's experiments, however, raise technical problems which make their interpretation difficult and which are considered in the discussion which followed his paper. For the present the existence of a hypnogenic centre must be regarded as not proven.

VI.—Prolonged Disorders of Consciousness in Man

We must now consider some disorders of human consciousness in the light of the facts and ideas derived from animal experiments. But though animal experiments can teach us much about the correlation between anatomy, physiology and the *behaviour* of the animal, they can tell us nothing about the *content of its consciousness.* In man, therefore, we enter a new field, where much is still unknown, and where often all we can at present hope to do is to ask the right questions. The psychological analysis of states of disordered consciousness is for the most part empirical and based mainly upon rough and ready clinical criteria; and most of the pathological causes of disorders of consciousness act in a diffuse or complex manner, or, if their action is focal, its nature is not fully understood. Consequently it is often difficult to establish the physiological disturbance underlying the patient's symptoms.

(i) *Disorders of Consciousness Resulting from Lesions of the Brain-stem and Optic Thalamus*

G. Jefferson (1944), French (1952), Cairns (1952) and M. Jefferson (1952), have described unconsciousness as a symptom of lesions of the brain-stem and optic thalamus. The importance of their observations lies in the evidence they provide that in man, as in animals, the integrity of these regions is essential to consciousness. It is rarely, however, that the lesions produced by disease are comparable with focal experimental lesions. The following case, therefore, seems worth recording.

(ii) *Report of Case*

History.—W. H., aged 46, hotel proprietor. On October 24, 1937, he was visiting a friend and looking at his friend's new car in the road. The friend turned round to find him clinging to the fence. He said "I can't move." He was assisted into the house, and within a few minutes was unconscious. A few hours later he was found to have dilated and fixed pupils, and there was a slight right hemiparesis, with an extensor plantar reflex on the right side. His blood pressure was 130/80. During the next six days he remained semiconscious: he was able to swallow and occasionally roused slightly. He had an irregular fever, his temperature occasionally reaching 101°.

His previous health had been good and two months before the onset of his illness he had been accepted for life insurance.

Examination.—October 30, 1937. His appearance was that of a person normally asleep, with quiet breathing and normal skin colour. He could be roused by vigorous shaking, and might even murmur a word or two, but at once relapsed into unconsciousness. The optic disks were normal. The pupils were moderately contracted, the left slightly larger than the right, neither reacted to light. There was a slight divergent squint. There was occasional twitching of the right lower face and he appeared to appreciate pin-prick slightly less on the right side of the face than on the left.

The muscular tone was normal on both sides. Spontaneous movements of the limbs were more evident on the left side than on the right. The arm-jerks were present and equal, the knee-jerks were almost absent and the ankle-jerks absent. The abdominal reflexes were not elicited, and the plantar reflexes were right ? flexor, left flexor. He responded to pin-prick equally over the limbs and trunk. There was no cervical rigidity and Kernig's sign was negative.

The blood pressure was 130/80, pulse-rate 120.

Investigations.—Both lateral ventricles were punctured by Mr. Northfield. Cerebrospinal fluid: from right ventricle, protein 35 mg., 3 cells, from left ventricle, protein 40 mg., 5 cells; lumbar fluid: protein 55 mg., 45 cells. W.R. in c.s.f. partial positive; in blood, incompletely negative. Ventriculograms: left ventricle normal, right ventricle, descending horn alone filled. Bilateral parietal taps by Mr. Northfield revealed no abnormality. Blood urea (Nov. 1) 0·153 mg. per cent. Urine contained 1/10 vol. albumin.

Course of illness.—On October 31 the patient had an axillary temperature of 101·2° and a rectal one of 105·5°. His coma deepened and he died on November 4, having been ill eleven days.

Pathological examination (Professor Dorothy Russell).—December 3, 1937: No. L.H. 56735. P.M. 567.1953 (Appendix).

The post-mortem examination had been carried out elsewhere and the available material consisted of the brain and portions of liver, pancreas and kidney: all fixed in formaldehyde.

Macroscopic appearances.—The brain has been divided coronally, before fixation, through the cerebral hemispheres immediately anterior to the optic chiasma and again through the brain-stem a little anterior to the trigeminal roots. The main cerebral arteries have been opened up: they are everywhere of normal appearance. The leptomeninges are thin and transparent except over the crura cerebri where they appear slightly opaque and matted. The meninges over the foramina of Luschka have been removed; the arachnoid of cisterna magna is thin and transparent.

An ill-defined area (2·1 × 1·4 cm.) of softening in the head of the left caudate nucleus extends ventro-laterally into the medial half of the internal capsule, where it contains closely-set punctiform and slightly more diffuse hæmorrhages, and anteriorly into a larger (2·1 × 1·5) hæmorrhagic area, the centre of which is extensively fissured and contains an irregular mass (0·6 cm. diam.) of recent clot, related to several needle-tracks.

Further coronal sections show extensive, partly discrete and partly confluent, anæmic softening in the hinder part of the hypothalamus extending into the mid-brain as far caudally as the level between anterior and posterior corpora quadrigemina. There is a well-defined elliptical area (0·5 × 0·3 cm.) of softening in the left thalamus, 0·5 cm. beneath ependyma of left wall of ventricle, its position being towards ventro-lateral border of the medial nucleus. At a distance of 0·25 cm. ventral to this is a

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horizontal band (0·7 cm. long × 0·2 cm. broad) of similar softening extending medially towards the orifice of the Sylvian aqueduct and dorsal to the substantia nigra on both sides. This band is continuous with a poorly defined area of greyish-yellow necrosis lying ventral to the aqueduct and dorsal to the substantia nigra of both sides. A transverse section of the mid-brain immediately anterior to the anterior corpora quadrigemina shows a symmetrical butterfly-shaped distribution of the necrosis, each being 1 × 0·8 cm. from side to side. It spares the subthalamic nuclei but clearly involved the red nuclei and nuclei of third nerves. At the coronal level of the anterior corpora quadrigemina the necrosis still affects both sides but is greater on the left where it extends ventrally to involve the medial third of substantia nigra and medial quarter of the crus (fig. 1).

Cerebellum.—There are ill-defined disseminated foci of friable brownish-grey softening (up to 1·5 × 0·3 cm.), mostly somewhat linear, occupying the cerebellar convolutions in the anterior parts of both lateral lobes, being most conspicuous where the cerebellum comes into relation with the incisura of the tentorium but also in the deeper folia more caudally. The vermis appears free. There are no further abnormalities in the brain.

Microscopical appearances.—In sections taken from the basal ganglia and brain-stem the softened areas are uniformly necrotic and infiltrated with considerable numbers of fat-granule cells. The adjacent blood vessels display no histological abnormality. The leptomeninges of the region contain a few small lymphocytes. Similar necrosis, accompanied by considerable focal hæmorrhage, is found in the cerebellar cortex. Many Purkinje cells have disappeared from the surface folia. There is also a patch of necrosis in the central white matter lateral to the dentate nucleus. A few arteries and arterioles in the surface leptomeninges have undergone fibrinoid necrosis.

Sections of the liver, pancreas and kidney show no significant changes. The arteries and arterioles are devoid of fibrinoid necrosis.

Comment.—The appearances in the brain are those of recent infarction. The reactive infiltration with macrophages agrees with the clinical duration of the neurological disturbance. But the vascular occlusion responsible for this lesion was unfortunately not demonstrated; it was probably embolic.

The cerebellar changes are also compatible with infarction, brought about by the rostral herniation of tissue through the tentorial opening with consequent nipping of branches of the superior cerebellar arteries against the free edge of the tentorium.

This patient's main lesion extended from the inner aspect of the left optic thalamus into the tegmentum of the brain-stem where it became bilateral and reached as far caudally as the junction between the anterior and posterior corpora quadrigemina. This lesion was of sudden onset consistent with an embolic origin. Its interest lies in the circumscribed character of the lesion and its symptomatology. Apart from minimal pyramidal signs, due no doubt to the involvement of the left crusta, the symptoms were those of parasomnia with profound and irreversible disturbance of consciousness. Thus both the lesion and its symptoms were similar to those described earlier in this review as producing a similar result when induced experimentally in animals. Unfortunately clinical electro-encephalography was in its infancy when the patient was seen.

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PLATE LVIII

FIG. 1.—Coronal section at the level of the anterior corpora quadrigemina showing necrosis involving the tegmentum on both sides and on the left side (the right in the figure) extending ventrally to involve the medial $\frac{1}{3}$ of the substantia nigra and the medial $\frac{1}{4}$ of the crus. Loyez stain.

To Illustrate article by Russell Brain.

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VII.—Unconsciousness in Relation to the Site of the Lesion

(i) *Reversible Loss of Consciousness*

Reversible loss of consciousness is one of the commonest of clinical phenomena. It is drug-induced in surgical anæsthesia, in therapeutic prolonged narcosis and after an overdose of a narcotic drug. It is seen in one of its simplest forms in concussion, but after a head injury the loss of consciousness may be either momentary with recovery almost equally rapid, or indefinitely prolonged. Intracranial tumour and cerebral vascular lesions also provide familiar instances of loss of consciousness followed, in favourable circumstances, by its gradual recovery. In epilepsy it occurs paroxysmally. We have still much to learn about all these familiar conditions. Although we have rough clinical methods for estimating the degree of loss of consciousness, in terms of the reactions of the patient, and can point to certain broad resemblances between patients recovering from coma whatever its cause, we know little about their differences in relation to their causes. Moreover, clinical experience encourages us to take for granted loss of consciousness as a result of a cerebral tumour or hæmorrhage, often without asking why it occurred in a particular case. Increased intracranial pressure as such is rarely, if ever, a sufficient cause of unconsciousness, for a very high cerebrospinal fluid pressure in hydrocephalus may co-exist with normal consciousness. Clinical experience suggests that in cases of cerebral tumour and hæmorrhage a direct or indirect disturbance or function of the diencephalon is probably the determining factor. Incomplete recovery of consciousness raises further problems, for when a patient "partially recovers consciousness" after a head injury for example, and remains indefinitely in that state, it is usually difficult to decide how far his condition is attributable to persistent damage to subcortical centres concerned with consciousness and how far to damage to the cortex or to the connexions between the two. Further EEG studies may illuminate this question.

Clinical experience, however, has led to the differentiation of certain characteristics of the state of unconsciousness in relation to the site and nature of the causative lesion.

(ii) *Lesions Near the Third Ventricle*

Akinetic mutism is a term first used by Cairns, Oldfield, Pennybacker and Whitteridge (1941) for a condition in which the patient lies with eyes open and muscles relaxed, unspeaking and without voluntary movement, but capable of responding in a voluntary manner to sufficiently painful stimuli and with amnesia for the period during which symptoms persist. Other cases have been reported by Cairns (1952) and Williams and Parsons-Smith (1951), amongst others. This syndrome is associated with a lesion in the neighbourhood of the third ventricle and is reversible

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if it is due to pressure which can be removed. The EEG abnormalities have been reported by Cairns, and Williams and Parsons-Smith.

(iii) *Expanding Hemisphere Lesions*

G. Jefferson and Johnson (1950) draw attention to the characteristics of coma produced by this and the two following categories of lesion. They argue that expanding lesions of the cerebral hemisphere, together with those compressing the hemisphere from without, cause coma by compressing the mid-brain above the tentorium. The features of such a coma are early drowsiness, a pulse which becomes slower as the pressure rises, and noisy respiration.

(iv) *Hypothalamic Lesions*

These, of which my case, reported above, is an example are characterized by a condition simulating a restless and uneasy sleep, from which it may be possible partially to arouse the patient. The respiratory and pulse rates tend to increase, and the temperature to rise.

(v) *Posterior Fossa Lesions*

The coma produced by these, according to Jefferson and Johnson, is that most closely resembling normal sleep, with quiet, and possibly abnormally slow, respiration. The blood pressure tends to rise.

(vi) *The Plantar Reflexes in Coma*

The behaviour of the plantar reflexes in coma is another common phenomenon which has been taken for granted without questioning its significance. The plantar reflexes may be extensor in coma from any cause, including an overdose of a narcotic, an epileptic attack, and sleep, and become flexor on recovery of consciousness, provided the lesion responsible for the coma has not permanently damaged either pyramidal tract. Assuming that an extensor plantar reflex indicates depression of function of the pyramidal tract, it is merely a verbal and not a physiological explanation to say that the function of the pyramidal tracts may be depressed in coma. If, however, unconsciousness is due to impairment of cortical activity resulting from a loss of reticulo-cortical impulses, this may be the physiological explanation also of the reversible depression of pyramidal function which manifests itself as extensor plantar responses.

VIII.—Paroxysmal Disorders of Consciousness

(i) *Grand Mal* and *Petit Mal*

The cause of the loss of consciousness in epilepsy still eludes us. When an attack begins with sudden loss of consciousness, with or without motor manifestations, as in *grand mal* and *petit mal*, we must suppose that the disorder of function underlying the attack immediately implicates a region of the brain concerned with the maintenance of conscious-

ness. For Hughlings Jackson these were "highest level fits," and we shall have later to consider the significance of this term. Evidence is accumulating that the EEG wave-and-spike rhythms characteristic of *petit mal* can be evoked by electrical stimulation of the intralaminar region of the thalamus (Lewy and Gammon, 1940; Jasper and Droogleever-Fortuyn, 1947). The significance of this is discussed by Hess (1954) who writes:

> "From brain regions at least overlapping with the above areas (from which sleep can be induced by appropriate electrical stimulation) Morison and Dempsey (1942) elicited their recruiting response. Jasper and Droogleever-Fortuyn (1947) and Hunter and Jasper (1949) induced the electrical and clinical signs of *petit mal* by stimulation. The question therefore arises whether these seemingly divergent results are due to different systems being excited by different methods of stimulation or whether some functional connexion exists between the above-mentioned phenomena. Impairment of consciousness is of course a common feature of both sleep and epilepsy. The activation of certain types of epileptic discharges through light sleep is another possible link."

Gastaut (1954) discusses the relationship between consciousness and EEG rhythms. The frequent absence of any close correlation between a paroxysm of wave-and-spike dysrhythmia and impairment of consciousness illustrates the complexity of the problem and Gastaut is forced to conclude that "if the diffuse system of projection (from subcortical structures to the cortex) plays a part in the regulation of cortical electrogenesis and the level of consciousness, these two factors are not directly dependent on each other and may evolve independently."

Even if in "idiopathic" epilepsy loss of consciousness is due to a disorder of function in some basal structure, we do not know what that disorder is. And we have also still to explain how attacks characterized by an initial loss of consciousness are brought about when the causative lesion is situated elsewhere, e.g. in the frontal lobe. Penfield and Jasper (1947) suggest that in such cases a unilateral focus fires into a more centrally placed area.

(ii) *Temporal Lobe Epilepsy*

Most of the symptoms of epileptic attacks originating in the temporal lobe were described by Hughlings Jackson. During recent years the work of Penfield and his collaborators has added to our detailed knowledge of their clinical features as well as raising the problem of the interpretation of the effects of stimulating this region in the conscious patient. Temporal lobe attacks are characterized by varied disorders of consciousness; impaired awareness, perceptual illusions, simple or complex hallucinations, disorders of recognition and memory, emotional disturbances, and automatic activity are the principal ones. Since Jackson's day, discussion has centred on the question, which symptoms are to be regarded as manifestations of the epileptic discharge and which as the

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result of what Wilson (1928) called "epileptic decontrol," i.e. the disorderly action of parts of the brain when higher levels, which normally control them, are temporarily out of action. We need not discuss this point in detail now, but it will probably be generally agreed that an olfactory hallucination is likely to be a symptom of an epileptic discharge; while automatic behaviour similar to that which occurs apart from epilepsy, e.g. after concussion, is probably a symptom of decontrol. Williams (1956) attributes the emotions which may occur in temporal lobe attacks to ictal discharges.

(iii) *Narcolepsy*

Hess has been quoted above as drawing attention to a possible physiological relationship between sleep and epilepsy, and the nature of narcolepsy calls for review in the light of the new knowledge acquired during recent years. Adie (1926) was emphatic in distinguishing narcolepsy from epilepsy, but clinical experience suggests that narcolepsy is a symptom rather than a disease, and supports Wilson's (1928) view that "any alleged contrast between the narcolepsies and the epilepsies is merely a contrast between symptoms, and leaves untouched the problem of whether or not there is a similar mechanism of production behind each." Wilson draws attention to the possible relationship between cataplexy and akinetic epilepsy, and Symonds (1954) concludes that "there is no fundamental distinction between epilepsy and cataplexy." It may be that narcolepsy when associated with cataplexy has a different pathogenesis from narcolepsy as an isolated symptom. The EEG in narcolepsy is reported to be normal, or that of normal sleep (Hill, 1955).

IX.—Hallucinatory States

No account of the physiology of consciousness would be complete without some consideration of the hallucinatory states, which present complex and largely unsolved problems (Brain and Strauss, 1955). Only two points, however, will be made now. Whether or not drug-induced hallucinatory states can occur without wider disturbances of consciousness, it is clear that in most neurological conditions, e.g. temporal lobe epilepsy, confusional states, hallucinations associated with sleep disorders, and Lhermitte's peduncular hallucinosis, the occurrence of hallucinations is associated with a more general disturbance of the processes of consciousness. The second point is the complex relationship which exists between sensory input and hallucinations. Hallucinations may be associated in a complex manner with pathological sensory loss (Lhermitte, 1951), with experimental sensory deprivation (Hebb, 1954), or with unusual sensory stimuli, e.g. flicker (Walter, 1953). Hebb concludes: "We must, it seems, recognize two distinct functions of a sensory event: it may arouse or guide a specific response; but it has also

a non-specific function in maintaining the normal waking organization of brain function."

X.—Head's Concept of Vigilance

It is of more than merely historical interest to consider at this point Head's (1926) concept of "vigilance." He introduces the subject thus:

> "We are accustomed to associate a violent injury to the head with loss of consciousness and other symptoms of concussion; empirically we are equally familiar with that curious unwitting state, which precedes the patient's complete recovery, during which he is liable to act apparently reasonably but in a pure automatic manner. But we make no attempt to explain how a local lesion of the brain can abolish certain specific mental activities, leaving other independent functions of the mind intact."

So it was disturbances of consciousness which led Head to formulate his concept of vigilance. He then turned to the divided spinal cord in man and the decerebrate animal for evidence of variations in the state of activity of the separated portions of the nervous system; which at some times shows more complex forms of behaviour than at others.

> "If we were dealing with an intact animal, we should say that these differences were associated with the presence or absence of consciousness. But such an explanation of the reactions of the spinal or decerebrate preparation is unsatisfactory, and I would suggest that we employ the word 'vigilance' for this state of high-grade physiological efficiency."

After discussing automatic actions, sensation, and the continuity of consciousness, Head turns to purposive adaptation, two cardinal features of which are that "the character of the response varies with specific differences in the quality of the stimulus and not only with its relative amount," and that "the form assumed by the reaction is determined more of less by the sequence of events and is not dependent solely on the excitation of the moment." He concludes that "such diverse and varying modes of response . . . demand a high degree of vigilance in the structures responsible for the particular reaction." From this he passes to a section entitled: "Psychical and somatic behaviour dependent on the state of vigilance of the nervous system." He draws implicitly, if not very explicitly, a distinction between two kinds of disturbance of consciousness.

> "These various mental activities, sensation, perception, imagery, symbolic formulation and ideation may be affected independently by an organic lesion because the physiological processes, which subserve them, are bound up with the vitality of different parts of the brain, any one of which can be destroyed without of necessity affecting the others. Each such local disturbance is associated with some specific psychical loss of function. But the activity of the mind as a whole is uninterrupted. The field of consciousness remains continuous as before." But, "consciousness stands in the same relation to the vigilance of the higher centres as adapted and purposive reflexes to that of those of lower rank in the neural hierarchy. When vigilance is high, mind and body are poised in

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readiness to respond to any event external or internal. But if it is lowered by injury, want of instruction, chloroform or other toxic influence, these high-grade functions may suffer in general or in part, whether they are associated with consciousness or not."

In considering Head's views on vigilance, we must bear in mind that they were his last words on neurology, expressed more than thirty years ago, and developed in relation to the problem on which he was then writing, namely aphasia. It would seem that, reflecting on the physiological problems presented by aphasia and viewing them in the light of Sherrington's ideas, he arrived at this new conception, which he had no opportunity to refine or develop on more general lines. In essence, he regarded vigilance as a state of the nervous system manifested at all levels and capable of either local *or general* depression; and "conscious processes . . . are the expressions of physiological vigilance."

The importance of Head's concept of vigilance is twofold. It is at the same time a physiological and a psychological function, and it is one which as underlying consciousness is capable of general depression. Sherrington (1940) accepted and applied Head's idea.

XI.—Consciousness and Integration

What has been said hitherto in this review shows how close an interrelationship exists between the cerebral cortex and the diencephalon and brain-stem in connexion with consciousness, but it is also possible to recognize a differentiation of function between them.

When we speak of consciousness we say we are conscious *of* something, which we may call the *content* of consciousness, and we know what we mean by this, whatever logical view of these statements the logicians may take. We are normally actually or potentially conscious of sights, sounds, touches, smells, etc., i.e. of sensations; of anger, fear, interest, excitement, etc., i.e. of feelings or moods; of memories and recognitions based on memories; of ideas and thinking; of images; of actions; of being sleepy and awakening from sleep. This list is not meant to be complete. In addition there are abnormal contents of consciousness such as disordered sensations, like pains and giddiness; disordered perceptions, such as illusions and hallucinations; disordered memories, and disordered ideational states, such as delusions.

(i) *Integration and the Reticular System*

There is certainly a clinical distinction between disorder of the content of consciousness and disorder of "consciousness itself." Most people indeed would not apply the term "disturbance of consciousness" to the disorders of the *content* of consciousness which the neurologist encounters many times a day—such symptoms as areas of anæsthesia, visual field defects, pains, paræsthesiæ, teichopsia, etc. These are not the sort of

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symptoms he has in mind when he speaks of a patient being "unconscious," "less deeply unconscious," "partially conscious" or suffering from "clouding" or "impairment of consciousness." This distinction is based on the fact that when a patient is suffering from blindness, pain or sensory loss, the rest of the content of his consciousness, actual and potential, is normally unaffected. But a patient who is unconscious has lost all capacity for entertaining any conscious state, and a patient with "impaired consciousness" usually shows a defective awareness of and reaction towards the contents of consciousness reaching him by any and every sensory channel.

Thus it is clear that consciousness may be affected as a process, as something of which there may be more or less activity. It is also clear that consciousness is in a number of ways an integrated whole. I have spoken earlier of the part which such integration plays in perception and attention. Other modes of integration are that of percepts with feeling in relation to action, and temporal integration, in which the present experience is linked with the subject's past, and with those processes which will enable his present to become in future part of his recallable past.

It is precisely these integrative functions which to a greater or less extent and in mutually varying degree are impaired in those states which we describe as states of impaired consciousness, and in many hallucinatory states; and loss of perceptual integration, emotional integration and temporal integration are all frequently exemplified in attacks of temporal lobe epilepsy.

There is much evidence that this kind of impairment of consciousness is produced by damage to an area of brain extending from the region of the third ventricle through the posterior hypothalamus and tegmentum of the brain-stem down to the medulla; whereas it does not occur as a result of damage to most of the cerebral cortex. The temporal lobe is in a peculiar position, since here it is discharging and not destructive lesions which in man at least produce these disorders of consciousness. We do not know the effects of bilateral temporal lobectomy in man, but we know that bilateral lesions of the hippocampus cause complete amnesia for recent events (Scoville and Milner, 1957), and that bilateral temporal lobectomy in monkeys causes severe perceptual and emotional disturbances (Klüver and Bucy, 1939). Hence there is ample evidence to support the view that the area of the diencephalon and brain-stem just mentioned is necessary for the maintenance and integration of consciousness, and the temporal lobes also appear to play a part in this process which is distinct from that of other cortical areas. This is the valid basis of Penfield's (1952) concept of the Centrencephalic Integrating System. It will be clear from this review that I do not follow Penfield in attributing to the centrencephalic system many discriminative motor,

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sensory and mental functions hitherto generally regarded as mediated by the cortex. Nevertheless recent work on conditioned reflexes (Gastaut, 1958; Jasper, Ricci and Doane, 1958) shows that the reticular formation, especially the thalamic part, does exercise some discriminative functions, and that the difference of function between reticular formation and cortex may be less clear-cut than has sometimes been thought. It also emphasizes their interdependence.

(ii) *Integration and the Cerebral Cortex*

What is the role of the cerebral cortex in consciousness? All clinical experience suggests that cortical activity in relation to consciousness is predominantly concerned with its content. Since the organization of cortical function is fundamentally sensorimotor, it contributes to the content of consciousness primary perceptual data in relation to action upon perceptual objects.

> "The receptive function of the cerebral cortex is to provide us with a symbolical representation of the whole of the external world, not only distinguishing objects by their qualities, but also conveying to us the spatial relationships which exist between them, and at the same time giving us similar symbolical information about our own bodies and their relationship with the external world. All this information, of course, is given us not merely for the sake of pure awareness or contemplation, though that may sometimes be a by-product of it, but in order that we may act, hence it is linked, in ways with which we are familiar, with the motor activities of the brain. This is the element in consciousness which for convenience of brevity we may call 'cortical' " (Brain, 1950).

As we have seen, this cortical contribution to the content of consciousness involves its own integrative processes, upon which perception and attention depend, and we may add temporal integration also, since all the evidence suggests that memory and recognition are based upon cortical processes.

Thus one important function of the cerebral cortex is the integration of those neural processes upon which consciousness depends, but this cortical function of integration in turn depends upon the integrity of diencephalic and brain-stem activities. Hence damage to the diencephalic–mid-brain processes causes a disintegration or actual loss of consciousness. Are we then entitled to say that consciousness is integrated by, or localized in, either the reticular formation or the cortex, or that the functions of one are "higher" than those of the other?

XII.—"Higher" and "Lower" in the Nervous System

Hughlings Jackson (1931–32) to whom we owe the notion of "levels" in the nervous system, distinguished three of these (H. J., I, 413–4).[1] The first consisted of the cord, medulla and pons which he held represented

[1]The references to Hughlings Jackson are to the volumes and pages of the Selected Writings.

"simplest movements of all parts of the body by a series of lowest motor centres." The second level "is composed of centres of the Rolandic region (so-called 'motor region' of the cerebral cortex), and possibly, of the ganglia of the corpus striatum also. It represents complex movements of all parts of the body from eyes to perineum (re-represents)." The third or highest level "is made up of centres of the præfrontal lobes (highest motor centres, motor division of the 'organ of mind'). It represents most complex movements of all parts of the body from eyes to perineum (re-re-represents). The highest centres (sensory and motor divisions of the highest level)—the 'organ of mind,' or anatomical substrata of consciousness—are the acme of evolution; they have the same kind of constitution as lower centres, they are sensori-motor as certainly as the lumbar enlargement is (of course each level is bilateral)." And he held that fits which are characterized *ab initio* by loss of consciousness or "highest level fits," must in many, but not all, instances be "produced by excessive discharges beginning in parts of the præfrontal lobes, highest level (motor province) of the cerebral system (H. J., I, 415). Jackson distinguished between what he called the "anatomically highest" and the "geographically highest" centres (H. J., I, 139). In the passage just quoted he was speculatively locating the anatomically, i.e. functionally, highest centres geographically in "the præfrontal lobes."

On a certain view of localization a case could be made out for that belief today in the light of our knowledge of the functions of that part of the brain, especially as they are revealed by leucotomy. But it has become increasingly difficult to accept the idea that cerebral function is "localized" in that area, destruction of which interferes with its exercise. A more holistic view of the activity of the cerebral cortex seems more satisfactory. It is true and significant that the conscious patient in whom a movement is evoked by electrical stimulation of the motor cortex does not feel as though he had himself willed the movement—a point which much impressed Sherrington (1950). But if we are to seek the cerebral basis of the will, even in the simplest sense of those activities of the brain through which the whole personality operates to bring about an action, we can hardly localize them in the prefrontal lobes, but must suppose them to involve all those regions through whose activity ideas, memories, and feelings, are experienced, and plans for action entertained, i.e. large areas of the cortex.

Our present knowledge suggests that the pathogenesis of Jackson's "highest level fits" is more complex than could be known in his day. While it is true that loss of consciousness, implying loss of function of "the organ of mind" is the initial manifestation, the evidence suggests that this is probably the result of a diencephalic disturbance. What conclusion are we to draw from this?

Some neurosurgeons have drawn attention to the fact that removal of

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large areas of the cortex has no apparent effect on consciousness, and this has been held to imply that the cortex cannot carry out the important functions just attributed to it. Here we encounter again the problem of localization. If cortical functions in general are "localized" even in the sense in which localized damage to the motor or sensory cortex causes motor or sensory defect, we should expect localized removal of areas of cortex to cause localized deficits in the psychological sphere. But if cortical functions are not localized in this way, apart from certain receptor and effector terminal areas, we should not expect any such result. Lashley's (1952) experiments have shown that the parastriate areas and "almost all other parts of the neo-cortex of monkeys" can be separately removed "without significant disturbances of visual perception or memory." This does not necessarily mean that these functions are "localized" elsewhere than in the cortex, but it seems more likely to mean, as Lashley suggests, that we lack at present the theoretical concepts necessary to explain a "generalized" representation of perceptual and mnemic patterns in the cortex. In the present state of our knowledge, therefore, we should be unwise to reject the view that the cortex plays an integral part in the "highest level" functions.

But in what sense are they "highest"? Jackson called them "the acme of evolution," and Sherrington (1940) says: "Our roof-brain is the latest, and crowning, organ of our nervous system." Clearly what both these writers have in mind in speaking thus is that the expanding cerebral cortex has been the basis of the evolutionary development of all those perceptual, motor and ideational functions which give man his unchallenged supremacy as the "paragon of animals."

But how far is it justifiable to consider "higher" either in space or value a concept of cortical function which is necessarily an abstraction from the unity of the nervous system? Little is known about the role of the cortex in relation to emotion: its function is perhaps mainly inhibitory, but it seems probable that those nuclei and pathways upon which the quality and richness of our feelings depend are diencephalic, and closely related to autonomic centres, and the nervous regulation of the endocrine system. Sherrington (1940) writes:

> "The neural basis of affect we can suppose need not entail much neural superstructure. It might use chemical reinforcement. This lets us stress the roof-organ of the fore-brain as especially cognitive, with below it the old kernel-organ of the fore-brain especially related to 'affect'; and we remember that every cognition has, potentially at least, an emotive value; emotive, and, along with that, conative effort as a further factor."

These words may make us wonder if there is any meaning in asking whether the cortex or the diencephalon of an artist or a poet, or indeed of any human being, is the "higher," and whether we should not conceive of the relationship between these two parts of the brain, not as

a hierarchy, but as an integrative unity such as that represented by the *yin* and *yang* symbols of Taoism intertwined in their self-embracing circle.

This review necessarily leaves much unsaid, and I have not discussed the most important question of all—the relationship between brain states as such and consciousness. This is not a neurological question: whether as a metaphysical one it is soluble we need not now enquire. There can be little doubt, however, that much progress should be possible in our knowledge of the relationship between brain states and conscious states. In Lashley's (1952) words:

> "The finer details of cortical structure must be investigated, both the nature of the network in functional areas and the modes of interconnection between areas, in order to clarify the nature of the patterns of neural activity which they can mediate. The psychological data must be analysed, not in terms of formal logic, which has been the customary procedure, but with reference to the patterns of activity which they represent. It is only by such co-ordinated effort that the ultimate synthesis of neurology and psychology can be brought about."

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NOTICES OF RECENT PUBLICATIONS

VIRAL ENCEPHALITIS

Viral Encephalitis. A Symposium of the Fifth Annual Scientific Meeting of the Houston Neurological Society, Texas Medical Center, Houston, Texas. Compiled and edited by WILLIAM S. FIELDS and RUSSELL J. BLATTNER. 1958. Pp. 225. Springfield, U.S.A.: Charles C. Thomas. Price 52s. 6d.

This well-produced volume, published with the financial support of a group of American pharmaceutical manufacturers, presents six papers on viral encephalitis, and the discussions which followed them, from a symposium held at Houston in 1957. Many of the conditions described—such as Equine, Japanese B, and St. Louis encephalitides—are of only theoretical interest to most British readers, and, not unreasonably in view of the uncertain and probably indirect nature of their relationship to the preceding virus infection, the group of para-exanthematous encephalomyelitic illnesses with which we are more familiar here is treated cursorily.

A considerable part of the work deals with epidemiological and immunological considerations in relation to arthropod-born virus infections which are again of limited interest to a physician not in contact with cases of this kind. A certain paucity of clinical detail in this section—a common point of criticism of American literature of this kind—must here at any rate be attributed mainly to the non-specific and rather amorphous nature of these illnesses from the symptomatological aspect.

Probably the most valuable chapter from the clinical as well as from the pathological point of view is a comprehensive account of the pathology of "viral diseases characterized by the finding of nuclear inclusions," contributed jointly by Webb Haymaker, Margaret Smith, Ludo van Bogaert and Coleman de Chenar. This runs to more than a hundred pages, and is illustrated by twenty-nine excellent plates reproducing more than seventy photomicrographs. It describes in detail the clinical and pathological manifestations of acute herpes simplex infection in neonates, infants, and adults; and also furnishes a comprehensive account of subacute inclusion encephalitis, which is accepted by these authors as essentially similar in nature to subacute sclerosing leuko-encephalitis. The possible attribution of these syndromes to smouldering herpes simplex infection is discussed at length. No unanimity is reached on this subject by the authors, nor on the relationship between acute and subacute inclusion-body encephalitides in general.

This stimulating and useful book could be published only in the United States, not merely because of the expense of presenting such a wealth of topical

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information in so elegant and permanent a form, but also because the extended medical symposium, given by experts for experts and particularly appropriate for the presentation of work on the fringe of medical knowledge, is a typical and still almost uniquely American form of medical communication.

HENRY MILLER.

METABOLISM OF THE NERVOUS SYSTEM

Metabolism of the Nervous System. Edited by DEREK RICHTER. 1957. Pp. xiv + 599. London: Pergamon Press. Price £5.

The Second International Neurochemical Symposium was held in Aarhus in July 1956 and this volume is a record of the papers given, edited extremely well by Dr. D. Richter.

The general topic was the metabolism of the nervous system. This was considered from the molecular level, from electrolyte considerations and from the processes which involve lipids, nucleic acids and proteins, to mention but a few of the subjects discussed. The general arrangement was that a series of short papers followed one or two reviews on the theme of each session.

Neurochemistry is a rapidly advancing field and although clinical neurology as such is hardly mentioned, there are so many points of interest to the clinician in this volume that it is well worth the time taken to read selected portions.

To the neurochemist this volume is essential in order to give him an up-to-date view on cerebral metabolism. It is not possible to review each section adequately, and in any case some sections are more attractive than others, either because the reviewer works in that field or because there is a greater lucidity of expression shown by the writer. This is unavoidable in such a composite book but it in no way detracts from its general excellence. This volume can be thoroughly recommended to all interested in the subject.

J. N. CUMINGS.

ATTEMPTED SUICIDE

Attempted Suicide. Its Social Significance and Effects. By E. STENGEL and N. G. COOK. 1958. Pp. 136; 2 figures, 33 tables. London: Chapman and Hall. Price £1 5s. 0d.

This is the fourth of the Maudsley Monographs, and describes investigations carried out under the direction of Professor Stengel at the Maudsley Hospital over a number of years. To the material of 630 patients, obtained from the Maudsley and Bethlem Hospitals, observation wards and a general hospital, and broken up into five groups, a sixth group of 117 successful suicides from a coroner's court was added. The previous histories and the follow-up records of the patients, as well as their social relationships, were studied; and the reaction of society to the attempt, and the consequences that followed, are described.

The principal conclusion drawn is that attempted suicide is, psychologically, a very different phenomenon from successful suicide. It often represents an appeal by the patient for the attention of society, and sometimes also the deliberate facing of an ordeal. Society reacts to the unspoken appeal and

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help is often forthcoming after such an attempt which had previously been denied. Only a very small proportion of persons who had attempted suicide make at a later time a second and more successful attempt.

A wealth of statistical information is provided, which is of value since earlier investigations have been much more into the subject of suicide than attempted suicide. The principal defect of the work is that these statistical results are insufficiently integrated, so that a large part of them do not attain the appearance of having much importance or meaning.

ELIOT SLATER.

PSYCHOLOGICAL ASPECTS OF PEPTIC ULCER

On the Significance of Psychic Factors in the Development of Peptic Ulcer. By WILLY HØJER-PEDERSEN. 1958. Pp. 232. No price stated. Acta Psychiatrica et Neurologica Scandinavica Supplementum 119 Copenhagen: Ejnar Munksgaard.

Starting from a psychoanalytic viewpoint of, it would seem, an orthodox Freudian kind, the author has attempted to investigate the psychological problems of peptic ulcer by means of a controlled statistical study. His methods involve free and controlled interviewing, use of questionnaires, intelligence and projection tests, and social enquiries. His subjects consisted of 70 ulcer patients, of whom 51 suffered from duodenal ulcer and made up the nuclear group, and 51 controls, who were volunteers from the employees of the Kommunehospitalet. All were males. The two groups of patients and controls were alike in age distribution, marital state, birth-place and training; but occupationally the control subjects were more securely placed.

Some interesting differences were then found. The patients came from poorer homes, with higher family incidences both of peptic ulcer and psychiatric abnormality; they were more frequently of leptosome habitus; more of them were heavy consumers of alcohol or tobacco. On the psychiatric side, abnormal parent fixations were found in 50 out of 51 patients, in 36 out of 51 controls; conflict situations were much commoner with the patients; and 45 patients had had "manifest neuroses" as compared with only 20 control subjects. This last judgment seems to have been a somewhat subjective one, covering states, chronic, remittent, or intermittent, "in which the main symptoms were vague or vaguely defined anxiety, physical and psychic fatigue and dysphoria"; from an objective standpoint, 2 of the patients and 8 of the controls had previously seen a practising psychiatrist.

The author considers that his findings support the theory of Alexander, which is that repressed oral-receptive tendencies occur as stimuli to the stomach.

ELIOT SLATER.

SHORTER NOTICES

Der Kopfschmerz. Differentialdiagnostik und Therapie für die Praxis. By Dr. HARTWIG HEYCK. 1958. Pp. 301. 9 Figures. Stuttgart: Thieme. Price DM. 29.70.

This thorough little monograph to which Professor H. Krayenbühl contributes a foreword is designed to acquaint general practitioners as well as specialists

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in medicine and neurology with modern advances in the differential diagnosis and treatment of headache, "perhaps the commonest complaint in modern civilized states; 4–8 per cent of the population at one time or another seek medical advice for it." There are detailed accounts of migraine, facial and cranial neuralgias, and head and facial pain due to cervical lesions. Each chapter ends with an extensive and international list of references. That psychogenic causes are given the least space (4 pages) although they account for perhaps the largest number of patients shows that this aspect is still little understood.

R. A. HUNTER.

The Neurological Basis of Behaviour—Ciba Foundation Symposium. 1958. Pp. 387. London: J. & A. Churchill. Price 52s. 6d.

This symposium, held to commemorate the centenary of Sir Charles Sherrington's birth, was timely in another way, for it coincided with the first results of the concentration of interest in the "neurology of psychology," which was first stimulated by study of frontal and temporal lobe function, and then of the effects of rhinencephalic and mesencephalic lesions upon alerting and total behaviour. It is no exaggeration that this collection of nineteen essays is of first importance to those studying the physical mechanisms which serve and modify animal behaviour, particularly because they integrate personal observations into the general basis of relevant knowledge. Mention of essays by H. W. Magoun, J. C. Eccles, Philip Bard, M. Monnier, Wilder Penfield, H. Klüver, C. P. Richter, J. D. Green, Henri Gastaut and H. H. Jasper is justification for that claim. Each essay can be read independently, and the small type used for the subsequent verbatim discussions encourages the reader to go straight on to the next.

Integrating the Approaches to Mental Disease.—Two Conferences Held under the Auspices of the Committee on Public Health of The New York Academy of Medicine. Edited by H. D. KRUSE, M.D., Executive Secretary, Public Health Committee, New York Academy of Medicine. 1958. Pp. 393. London: Cassell & Co. Price 75s.

About fifty well-known workers in psychiatry and allied field met in two conferences, the broad aim of which "was to afford an opportunity to a group of experts who hold different views on the causality, pathogenesis, and therapy of mental disease to come together to engage in close examination and to plan research in common." The scope of their discussions is reflected in the subjects of the four opening papers on the ætiology of mental disorder, which covered its organic, experimental psychological, psychodynamic and psychosocial contributions. The large number of short formal papers make stimulating reading, but the verbatim transcript of the discussion which followed each is inevitably disjointed and tedious, and rather savours of a psychiatric interview. It has been included probably "for the record" rather than for the reader.

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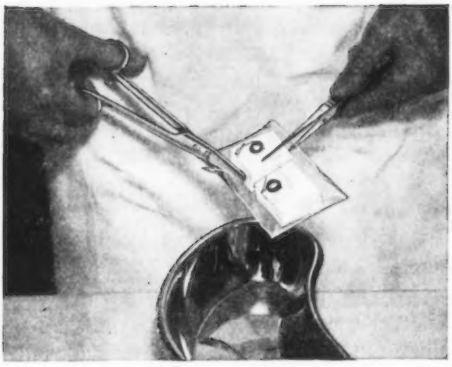

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